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The Effect of Aging and of the Development of Disease on the Ballistocardiogram

A Study of Eighty Subjects, Originally Healthy, Followed from Ten to Fourteen Years

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Second ballistocardiograms were taken on 80 subjects who were part of the series from which the original normal standards were secured in 1937, 1938 and 1939. Sixty-five of these subjects had retained good health during the long interval; by a comparison between their old and new records, the effect of "normal" aging on the ballistocardiogram has been determined. Fifteen subjects lost their health during the interval and two of them have died since the second test. The evolution of their ballistocardiograms has been compared with the development of their disabilities.

THAT older persons usually gave ballistocardiograms of smaller amplitude than young ones was realized early in the studies made in this laboratory. As a result, the estimate of cardiac output made from measurements of I and J wave areas diminishes with age, and so Tanner's normal standards[1] are adjusted for age.

Experience has also demonstrated that gross abnormalities of ballistic form are common in older persons,[2] but altogether absent or very rare in healthy young adults. Obviously, therefore, we had every reason to believe that there was a progressive change in the ballistocardiogram as age advanced, even though health commensurate with one's age might be retained. The present study was primarily designed to investigate the effect of aging on the ballistocardiogram of healthy persons with greater exactitude, to define the normal more exactly, and to obtain new information about the evolution of this record as disease began and advanced.

Certain data bearing on these interests were already available. In our files are the records secured on 200 healthy adults of all ages during the years 1937, 1938 and 1939.[3] This series could now be edited by the subtraction of all those who became sick in the intervening years, leaving us with a series of over 100 healthy persons with whom we are still in contact. In these, good health could be defined as a state in which no serious illness of any kind occurred within a period of 10 years, a definition that we regard as very rigorous and satisfactory. Tanner made use of these data in his study[1] and we have drawn upon them for part of this study. They permit a comparison between results secured in certain healthy young persons with those obtained in other healthy older persons.

But it seemed evident that even more interesting information concerning the effect of aging and of incipient disease on the ballistocardiogram could be secured by repeated tests

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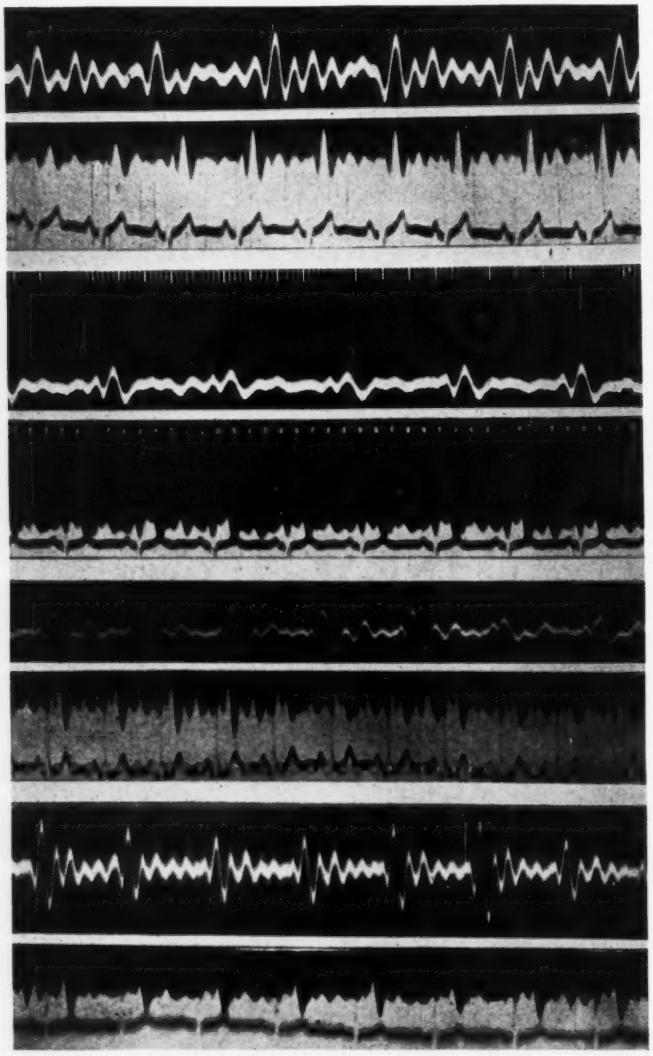


FIG. 1. Ballistocardiograms taken before and after a 10- to 14-year interval, a pair of records for each of four subjects. The reproduction is one-half actual size.

Changes of technic during the long interval have changed the appearance of the records making comparison by inspection difficult: The single edge (black above white) of the lower record of each pair corresponds to the upper margin (also black above white) of the upper record of each pair.

The time record on the third ballistocardiogram, the longest interval 1.0 second, applies also to the first and fifth ballistocardiogram, numbering from above downward. The time record on the fourth ballistocardiogram applies also to the second, sixth, seventh, and eighth ballistocardiogram. In these later records the film ran slower than in the earlier ones and allowance must be made for this when inspecting them.

The calibration of all the ballistocardiograms is the same: 280 Gm. displaces the light spot 1.0 cm., so the amplitude of each record is directly comparable.

A simultaneous electrocardiogram, lead II, is on the second record of each pair.

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on the same subject as he was growing older. Accordingly, in the fall of 1950 and the winter of 1951, we asked every member of our original series, whose address we knew, to return for a second ballistocardiogram, and we eventually secured such "follow-up" records on 80 persons who had been similarly tested from 10 to 14 years before. The changes in the ballistocardiograms of each individual and their relation to changes in his or her health during this period forms the chief subject of this presentation. We have found that when health is retained the ballistocardiogram changes slowly as age advances; if health is lost, it is likely to change rapidly. A preliminary report[4] has been made concerning certain features of this work.

Methods

From the subject's viewpoint, the test made over 10 years before was repeated exactly. The same ballistocardiograph was used to obtain both *old* and *new* records. In both series no records were taken within two hours after a meal, and the subjects lay at rest for at least 15 minutes on the ballistic table before a record was secured. Auscultatory estimates of blood pressure were made in both series, either just before or just after the ballistocardiograms were taken.

But certain elements of our technic had been changed in the long interval. Simultaneous electrocardiograms, recorded on the same film with the ballistocardiograms, were taken in all the new records, but only occasionally in the old ones. In both new and old records the calibration was the same, 280 Gm. deflecting the record 1 cm. Each of the new records was calibrated by a new device that allowed a weight of 280 Gm. to pull horizontally on the table for a short period, deflecting the record base line 1 cm., if the adjustment was at the usual standard, and giving an effect much like that of the usual calibration of electrocardiograms.

The technic of photography changed in the interval between the groups of tests, and examples of both methods can be found in figure 1. In the old records a wire was photographed so that the movement of a light streak on a dark background was recorded. In the new records, because of the simultaneous electrocardiogram, we photographed an edge, so that one side of the developed film is dark, the other side light, and on this light side the electrocardiogram is thrown. The moving line of the ballistocardiograms taken by the newer technic corresponds exactly to the upper edge of the ballistocardiograms of the older records, the edge from which measurements were always made. But inspection of the two types of records side by side, as in figure 1, is somewhat deceiving; one is likely to judge the old records to be of greater amplitude than the new ones, when the measurements show them to be equal. This is because one unconsciously tends to assess the amplitude of the old record not from the movement of one edge, as is correct, but from the highest peak of the upper edge to the lowest trough of the lower edge. Because of this difficulty, inspection of the actual records shown in figure 1 may be somewhat deceiving, and in figure 2 we resorted to scale drawings in which accurate comparisons can be made by inspection without optical illusion.

The speed at which the film was run also changed in the long interval. We now use a film speed closely similar to that of standard electrocardiographic technic; for the old records the film was usually run faster, another point which makes it difficult to compare new and old records by inspection alone.

With a record before us for the first time we inspected the whole of it and selected one complex as typical of the largest complexes of the respiratory cycle, and another as typical of the smallest complexes of this cycle. Only these two complexes were measured, and by averaging the heights and durations of similar waves of each an *average complex* was estimated. In the upper left of figure 2 this method is illustrated.

Measurement was made according to our usual routine. A base line was selected by inspection, the line the record would occupy if the heart stopped beating, and the vertical heights or depths of the H, I, J, and K waves were measured from this base line by the millimeter scale photographed on the record. We usually contented ourselves with reading to the nearest millimeter. The duration of the waves was measured in 0.01 second, along the base line,

Fig. 1., *Continued*

First Pair: records of L. G., the upper taken at age 33 and the lower at age 47. The blood pressure was 105/70 and 105/70 at the two tests. He has maintained good health.

Second Pair: records of N. O., age 48 and 62 years. His blood pressure was 120/88 and 165/110. He has developed hypertension.

Third Pair: records of N. L. J., age 54 and 67 years. The blood pressure 128/76 and 135/85. She believed herself to be in good health, and a complete cardiac study was negative. Nevertheless the recent ballistocardiogram is far from normal.

Fourth Pair: records of P. E., aged 50 and 63. Blood pressure 136/80 and 165/85. He thinks of himself as in good health, but the deterioration of the ballistocardiogram is conspicuous.

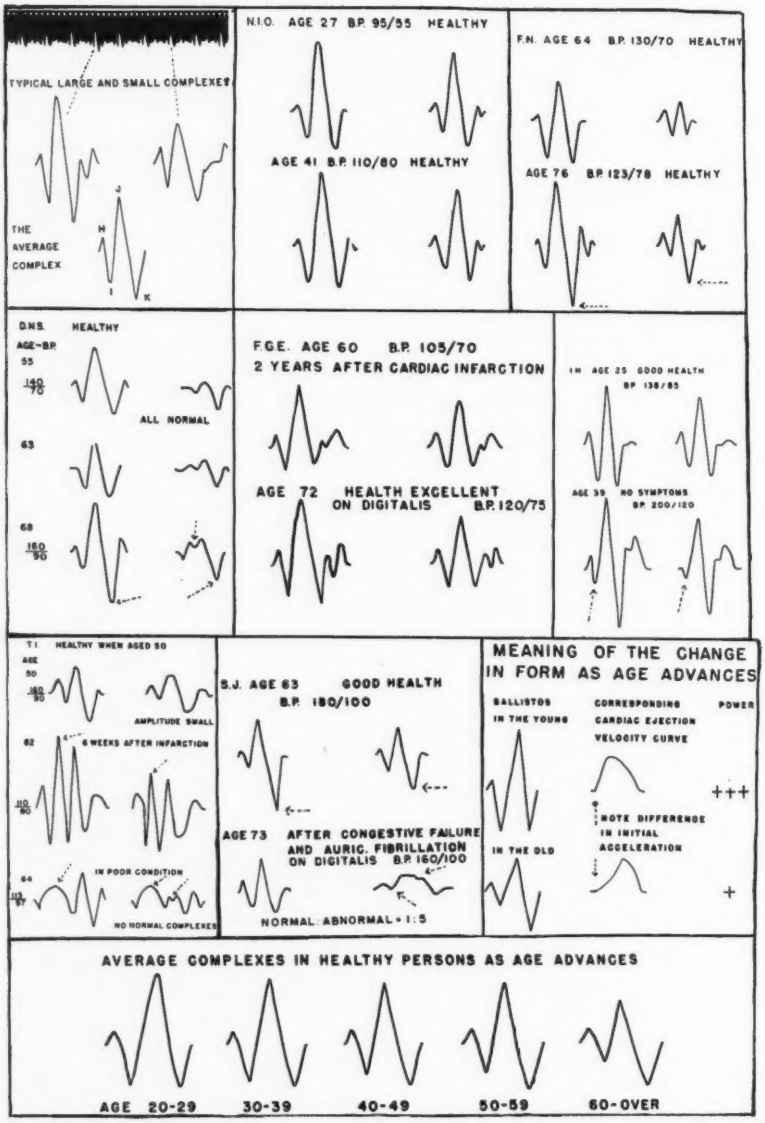


FIG. 2. Ballistocardiographic complexes drawn to scale to illustrate (1) changes in ballistic form occurring in typical healthy persons and patients during a period of from 10 to 14 years; (2) the average changes on aging; and, (3) their physiological explanation.

Top Row, Left: The relation of the enlarged drawings to the original ballistocardiograms. The average complex, defined as the mean of typical large and small complexes of the respiratory cycle. *Middle:* Typical large and small complexes of N. I. O., a healthy person. The complexes in the second record can be almost superimposed on those of the record taken 14 years before. *Right:* from F. N. who at age 64 gave a record looking younger than his age. At 76 the record looks older, but he is still in excellent health.

Second Row, Left: from D. N. S., who showed a prominent change in the smallest complexes during the 13 years. Arrows point to I wave displaced above base line and deep K waves. *Middle:* from F.

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by cutting out a piece of the time record and applying its edge directly to the distance being measured. As we readjusted the ballistocardiogram whenever the deflection of the light spot differed significantly from 1 cm. when the calibrating weight was applied, no correction of the vertical measurements was usually necessary.

The new records were measured in this manner soon after they had been taken. All the old records were found and remeasured except two. In these two cases we used the measurements recorded in the old record book for the I and J waves. Unfortunately H and K were not then being measured, so the averages recorded in the tables had to be obtained without these data. In a few cases items such as blood pressure or body weight were missing from the old records, deficiencies which account for the small differences in number of subjects in different tables.

The statistical analysis of the data was performed by standard methods as given in Snedecor's book.[5] The word significant is used throughout the paper in the statistical sense, meaning that the chances are over 95 in 100 that the difference is not due to chance selection.

Results

These can best be presented under two separate headings. Let us consider first the effect of aging on the ballistocardiogram as ascertained from records of those remaining in good health and, second, the effect of the development of disease as indicated by records of those whose health had failed.

Part I. The Effect of Aging When Health is Maintained

These studies can also be divided into two parts: first, those made on data secured from the ballistocardiograms of the old normal standard series, amended by the subtraction of all persons who had become seriously ill or had died since that time; second, those made on the persons on whom a second test was recently secured. Needless to say, the personnel of the two groups overlaps, for the first test made on all those tested twice is included in the old normal standard series in most cases.

The Effect of Aging as Estimated from Data in the Old Normal Standard Series

Ballistocardiograms were available on 27 men and 12 women aged from 40 to 49, 16 men and 7 women aged from 50 to 59, and 6 men and 3 women aged over 60 years, all of whom met the requirement of having been in good health when first tested and having survived for 10 years or longer after this test without serious illness.

The use of the I plus J distance rather than the measurement of single waves has the advantage that the considerable error of placing the base line is avoided. So in a recent publication[6] from this laboratory normal standards were set up for the vertical distance between the trough of the I waves and the peak of the J waves (the I plus J distance) of typical large and small ballistic complexes, as a measure of cardiac strength. These standards were derived from a statistical analysis of records secured on 100 young men and women of this series from 20 to 39 years of age. By this means equations were set up which predicted the value to be expected for any subject and the likelihood of any subject's measurements falling within the normal range. Unlike the standards for cardiac output as calculated from the ballistocardiogram, this standard was not adjusted for age, in the belief that it might be more valuable for that very reason, although this is certainly a debatable point.

So the effect of age on this feature of the ballistic record (the I plus J distance) was investigated by comparing the I plus J distance found in older subjects known to have remained healthy with that predicted from data obtained on the young.

FIG. 2, *Continued*

G. E., whose first record at 60 shows no effect of a previous cardiac infarct, and even at 72 he had a record looking younger than his true age. *Right:* from I. H., who developed hypertension. Arrows point to greatly diminished I waves.

Third Row, Left: from T. I., who developed serious cardiac infarction and eventually died. Arrows point to huge H waves during the acute stage, rounded bulky H waves and great distortion of smaller complexes later. *Middle:* from S. J., a hypertensive who went into congestive failure. Arrows point to deep K waves, contrasting with shallow I waves of early record; to the reduced I and distorted J of the later record. *Right:* A diagram to show our interpretation of the ballistic changes occurring during aging in terms of the heart's ejection velocity and power.

Fourth Row: Summary of our data on 65 healthy persons' average complex as age advances.

A very striking diminution of the I plus J distance occurs as age advances, the average deviations from the predicted values being −30 per cent, −40 per cent, and −49 per cent for those tested when in their 40's, 50's and 60's respectively. The difference between each of these means and the predicted value is highly significant.

The Effect of Aging as Estimated from Persons Retested after a Long Interval

In studying the data secured from these cases, the scope of the investigation was enlarged. We now aimed to discover the effect of aging not only on the amplitude of the record but also on each of the major waves of the ballistocardiogram, so we accepted the error of placing the base line and examined each wave individually. Also our criteria of what constituted good health were different.

The 65 persons stated that they were in excellent health. We realize that some of them might have deceived us. Certainly all were working actively and all had been known personally to the senior author for many years and gave every appearance of good health. Dr. Francis C. Wood most kindly volunteered to make a complete clinical study of the group. About one third have already been examined, and we plan a later communication on this aspect of our work.

Not all those admitted to this healthy group had completely negative histories. Thus there were several persons with pulmonary tuberculosis arrested for many years, one who has had an occasional attack of auricular fibrillation of short duration despite completely negative clinical findings at other times, and two who had had attacks somewhat suggestive of cardiac infarction but without any electrocardiographic confirmation. Two had taken minute doses of thyroid for many years on the advice of their physicians, although definite hypothyroidism had never been demonstrated. In several persons over 60 the blood pressure had crept up towards the hypertensive level. Especially in the older age groups, the distinction between health and disease is not always easy.

We were disappointed in the small number of persons, in their 20's when first tested, who could be secured for a second test 10 years later. The original group consisted mostly of medical students and hospital residents, and many had moved far away from Philadelphia in the interval.

Our first step was to investigate the effect of aging on the *average complex*. Before beginning the statistical analysis it seemed wise to make some adjustment for the effect of differences in size of subjects. So, without setting up a regression, we merely assumed that the wave altitudes would be related to the subjects' weight and surface area, tried both, and chose the latter. Accordingly the altitude of the waves for each subject was divided by the ratio of his or her surface area to 1.82, the latter the median surface area of the group in square meters. The statistics given in table 1 were calculated after this adjustment.

In table 1 the means of the heights and depths of the main ballistic waves of average complexes are given, for each decade of life.

TABLE 1.—*Effect of Aging on Mean Height and Depth of the Main Ballistic Waves as Estimated from the "Average Complex" of Each Subject, Adjusted to Surface Area 1.82 Square Meter.*

Group	No.	H Wave		I Wave		J Wave		K Wave	
		Mean altitude	σ	Mean depth	σ	Mean altitude	σ	Mean depth	σ
		mm.		*mm.*		*mm.*		*mm.*	
20–29	15	1.8	1.0	5.0	1.1	8.6	2.8	5.2	1.8
30–39	30	1.5	1.1	4.7	1.5	8.0	2.1	5.1	1.8
40–49	38	1.8	1.0	3.9*	1.2	7.6	1.9	5.1	1.6
50–59	26	1.8	1.0	3.7*	1.8	7.6	3.1	5.6	2.1
60–over	19	1.8	1.2	2.2*	1.2	5.4*	1.9	5.2	1.3

* Significantly different from 20–29 year mean.

In the table each subject appears twice, the first test being in one decade, the second in another.

In this table it will be seen at once that, although the mean amplitude of H and K waves does not change significantly, there is a steady tendency for the I and J waves to diminish as age advances. The asterisks indicate which means of the older groups are significantly different from the corresponding means of the 20 to 29 year group.

The results recorded in table 2 show a slight tendency for the I and J wave durations to diminish as age advances and their waves become smaller in amplitude, but the difference is never significant. There is also a slight tendency for the H and K waves to broaden and there is a special point here which will be discussed later, but again the difference is not significant because of the size of the scatter. So we found no significant effect of aging on the duration of any main wave of the ballistocardiogram.

TABLE 2.—*Effect of Aging on Mean Duration of Main Ballistocardiogram Waves as Estimated from the "Average Complex" of each Subject*

Group	No.	H Wave		I Wave		J Wave		K Wave	
		Mean duration	σ	Mean duration	σ	Mean duration	σ	Mean duration	σ
		sec.		*sec.*		*sec.*		*sec.*	
20–29	15	0.062	0.090	0.067	0.037	0.101	0.026	0.092	0.042
30–39	30	0.051	0.090	0.062	0.029	0.095	0.034	0.092	0.080
40–49	38	0.053	0.080	0.057	0.026	0.092	0.045	0.095	0.085
50–59	26	0.070	0.085	0.058	0.044	0.083	0.045	0.100	0.040
60–over	18	0.079	0.065	0.054	0.069	0.098	0.045	0.114	0.110

The means of the durations of the waves in older persons are not significantly different from the means of corresponding waves in the 20 to 29 year group.

Analysis by Paired Experiments

Having two estimations, made from 10 to 14 years apart on the same subjects, the data can also be handled in another way, which presents advantages when analyzed statistically. We therefore took the measurements of the H, I, J, and K waves of the typical large and small complexes on the records secured over 10 years ago and subtracted from them the corresponding measurements from the records secured recently. We thus obtained the changes found after aging for each main wave of both large and small complexes of every subject. The statistical analysis of these differences will be found in table 3, where it will be seen that, on the average, the I waves of the youngest group did not diminish as they grew from 10 to 14 years older, but in the older subjects this diminution on aging increased progressively, the mean change of the smaller complexes always exceeding that in the larger. Also the average diminution in the J wave on aging is seen to manifest itself only in the smaller complexes, while the H and K waves show no trend in the 10 to 14 year interval. But while the changes with aging in table 3 are consistent with those shown in table 1, only a few of the former reach statistical significance. Obviously the change of the ballistocardiogram with aging is so slow that a period of longer than 10 to 14 years would be necessary to detect it

TABLE 3.—*Average Changes in Ballistocardiogram Wave Heights as Healthy Subjects Aged from 10 to 14 Years*

Age at First Test	No.	Typical Large Complex								Typical Small Complex							
		H Wave		I Wave		J Wave		K Wave		H Wave		I Wave		J Wave		K Wave	
		Mean	σ	Mean	σ	Mean	σ	Mean	σ	Mean	σ	Mean	σ	Mean	σ	Mean	σ
		mm.		*mm.*		*mm.*		*mm.*		*mm.*		*mm.*		*mm.*		*mm*	
20–29	14	+0.36	1.5	+0.1	1.31	−0.07	0.67	+0.87	2.4	+0.68	1.08	+1.18	1.33	−1.0	2.3	+0.04	1.62
30–39	22	+0.75*	1.3	−0.4	1.8	+1.2*	2.3	+0.64*	1.1	+0.6*	1.1	−1.0*	1.5	−0.36	2.1	−0.2	1.8
40–49	17	+0.5	1.3	−0.3	1.8	+0.3	2.7	+0.6	1.9	+0.6*	1.1	−0.7	1.6	0	2.4	+1.0	2.1
50–59	9	+0.4	0.8	−1.5	2.0	+0.2	2.7	+1.1	1.8	+0.4	1.0	−1.9*	1.1	−1.1	2.0	−0.3	0.7
60–over	3	−0.7		−1.2		+1.7		+1.3		+0.27		+0.3		+1.9		+1.6	

* Significant for $p = 0.05$

with confidence in any healthy individual, or even in a small group of healthy persons.

In table 4 have been placed the average changes of pulse rate, blood pressure, and body weight which occurred in the same group of 65 healthy persons during the 10 to 14 year interval. The pulse rates of each individual tended to agree closely in the two tests and so there is no significant change in the averages of the different age groups. The average blood pressures show the well known tendency to increase

TABLE 4.—*Average Changes in Pulse Rate, Blood Pressure, and Body Weight in 62 of our 65 Healthy Persons Tested at Intervals between 10 and 14 Years.*

Age at First Test	No.	Average Change in Pulse Rate	Average Change in Systolic B.P.	Average Change in Diastolic B.P.	Average Change in Weight
		per min.	*mm. Hg*	*mm. Hg*	*lbs.*
20–29	10	+3.1	+4.7	+9.0	+12
30–39	21	+1.5	+1.6	+7.2	+7
40–49	19	+0.1	+10.1	+3.3	+3
50–59	9	+1.9	+10.0	+7.7	−8
60–over	3	−3.0	−4.3	−1.6	0

as age advances, and it is of interest that the average increase is greater in the older age groups excepting the oldest which, containing only three persons, neither adds nor subtracts anything significant, and is placed in the table only to complete the record. It is also of interest to note that the younger people tended to gain weight during the interval and the older ones to lose it; but the scatter is large and mean changes are not significantly different from zero.

Other Changes Found on Aging

In some cases in the later decades of life the I wave becomes not only diminished in size but displaced upward so that its point fails to pass the base line. Figure 1 gives three good examples of this and, in the three records of D. N. S. given in figure 2, the evolution of the abnormality could be followed. In the typical smallest complexes of the respiratory cycle when he was 55 the I wave, though small, clearly goes below the record's base line; when he was 63 it just touches the base line; when he was 68 its trough is well above the base line. Despite this developing ballistic abnormality this subject appeared to be in good health for his age and a careful and complete cardiac examination by Dr. Francis C. Wood did not disclose any abnormality detectable by the usual clinical methods of examination.

Such upward displacements of the I wave have been encountered only in the later decades of life in this study of healthy persons, but in records taken on the sick they are not uncommon. Thus we encountered them quite frequently in records secured soon after surgical operation[7] in persons over 50 years of age. The abnormality often disappeared as the patients recovered from the effects of the operation. We have as yet no conclusive data on its clinical importance, but the absence of anything similar in hundreds of records of healthy young adults arouses our concern for the future of those who have this abnormality.

A second change in contour developed by certain subjects when reaching their fifth or sixth decade is less conspicuous and probably less important. In these the L-wave peak fails to reach the base line, making K appear unusually broad. The smaller complexes of subject N. L. K. shown in figure 1 are good examples. We first became aware of this abnormality when measuring the duration of K waves, and in table 2 the average duration of K is increased in the oldest age groups because of its occasional presence, the duration of K having been defined as the time between the intersection of the JK downstroke with the base line, and the record's return to the base line.

It is of interest that these two changes with aging are in a way the reverse of one another; the first abnormality suggests a force pushing the record up at the beginning of systole and the second a force pushing it down at the beginning of diastole. In this clinical paper we will not pause to speculate about the nature and origin of these forces but, needless to say, the cases showing such abnormalities will be followed with unusual interest.

Normal Standards for the Contour of Ballistocardiograms

The statistics given in tables 1 and 2 may be used as empiric normal standards for the individual waves of the ballistocardiograms secured from high frequency instruments such

as are used in this clinic. To assess the normality or abnormality of any wave of the record of a patient being investigated one would proceed to measure typical large and small complexes in the usual manner, and average the heights and depths of corresponding waves. If the instrument's calibration differs from that we employ (280 Gm. displaces our light spot 1 cm.), one must make proportional correction for this. One then corrects for size of subject by multiplying each vertical measurement by 1.82 divided by the surface area of the subject concerned; the result can now be compared with the data in table 1 for subjects of corresponding age, the normal range being defined as some multiple of the standard deviation laid off on each side of the mean. Two is the multiple that convention has assigned for such defining the limits of normality but the convention arose under conditions very different from those of medical practice and smaller values might well be found more useful. And indeed, many abnormalities of ballistic contour are so obvious that they can be recognized with confidence by inspection alone. Nevertheless, the data contained in tables 1 and 2 define the contour of the records of healthy adults of different ages and permit us to go on with increased confidence to a study of the records of those who failed to maintain good health during the interval of years encompassed by our study.

Part II. Concerning Fifteen Subjects Who Failed to Maintain Good Health

In the light of the experience with aging in healthy persons, let us now consider the ballistocardiograms and the clinical histories of those whose good health did not continue. No attempt will be made to present all the cases who have been followed for over 10 years in this clinic. The cases here described are all persons whom we thought of as healthy when we invited them to come for the first test over 10 years ago.

I. *Persons Who Became Ill but Whose Ballistocardiograms Remained Normal*

Case H. N. P. was a housewife, 42 years of age when first tested in 1939. At that time she considered herself in good health save for an occasional attack of pollen or dust asthma which had started in 1930. She was known to be sensitive to a large number of substances, including dusts, foods, and pollens. In 1939 her ballistocardiogram was altogether normal.

In the 12-year interval the asthma has increased greatly in severity and on several occasions in recent years she had been forced to enter the hospital to be given oxygen. When tested in July, 1951, she was receiving epinephrine subcutaneously about 0.3 to 0.4 cc. about every four hours to keep her free of attacks, and was preparing to leave the city for the mountains to avoid the late summer pollens. Despite all this her recent (1951) ballistocardiogram was altogether normal and extraordinarily similar in appearance to the previous (1939) record; no wave measurement differed by more than 1 mm. from that of the record secured 12 years before. The similarity of pulse rates (70 and 76) and of blood pressures (120/70 and 120/64) in the two tests suggests she was not under the influence of epinephrine in the last.

Case K. J. M., a teacher, considered himself in good health when tested in 1939 when he was 42 years old. His ballistocardiogram was altogether normal at that time.

In 1943 he had a severe illness and was admitted to the hospital with what was diagnosed as Addison's disease. Since that time he has had the standard maintenance therapy for this condition which has been varied according to his needs. When tested in June, 1951, he was carrying three pellets, originally 75 mg. of desoxycorticosterone each, which had been implanted in his back on Jan. 20, 1951. He was also taking 6 mg. of cortisone daily, and 20 mg. Paredrine three times daily by mouth; and extra salt with his meals. He was working actively and considered himself in reasonable health. His blood pressure at the time of our test was 130/85, almost exactly what it had been before he became ill. The ballistocardiogram was altogether normal and indeed the I and J waves of the last tracing averaged 1 mm. larger than those of the preceding one, despite very similar pulse rates, 67 and 70, at the two tests.

Both these subjects have therefore suffered from severe and prolonged ill health without any detectable deterioration in their ballistocardiograms.

Case F. G. E., a doctor, long in medical practice, was first examined in 1939 when he was 60 years of age. At that time he gave a history of an attack of cardiac infarction two years before. He never thought of himself as seriously ill, but consultation with the physician who had cared for him, an old friend of the senior author, disclosed that there was no doubt whatever concerning diagnosis and that the electrocardiogram had been typical of this condition. Despite this history his ballistocardiogram in 1939 (fig. 2) was not only altogether normal but looked like that of a much younger man. At that time this result was thought of as being an instance

when the ballistocardiogram had failed to detect cardiac damage which was almost certainly present.

But during the 12-year interval the subject's health has remained excellent, with one reservation. Two years ago he went into auricular fibrillation and remained in this arrhythmia for several weeks, reverting spontaneously to normal rhythm. He was started on digitalis at this time and has continued to take it, although the arrhythmia has not recurred. In contrast to this transient episode of ill health let me put the fact that within the last few months, at the age of 72, he made an 82 on one of Philadelphia's most difficult golf courses. Taken in 1951, his ballistocardiogram differs from the previous record only by the changes characteristic of aging. It still looks like the record of a younger man.

In this case a normal ballistocardiogram was followed by continuing good health despite an ominous history.

Among those who have had their difficulties and maintained normal ballistic records we must also mention B. I., a female subject, in good health when first tested at the age of 28, who has proudly borne five healthy children in the 14-year interval. Her ballistocardiogram after all this, completely normal, can be almost superimposed on that secured during nulliparity.

II. *Subjects Attaining Advanced Age*

Case K. V.'s first record, taken in 1938 when she was 74 years old, was reproduced in a previous publication.[8] It was normal in form but extremely small in amplitude. She developed mild but typical angina pectoris on exertion about four years later and has had occasional attacks since.

This patient is still alive, aged 87. She has continued to suffer from arthritis of the knees, which has increased in severity, and she now is able to walk only a few steps on crutches. She is very feeble and spends much of the day in bed, the rest in her wheel chair. Leading this restricted life, she has not had an anginal attack for over a year. The ballistocardiogram taken in 1951 resembles the earlier one in that it is still of extremely small amplitude, but the form has now become highly abnormal. In the majority of complexes the H wave dominates the excursions, in the smaller complexes it is double the height of J; in many complexes I does not reach the base line; in many J is less than 1 mm. in height. No complexes could be passed as normal.

Case F. E. S., a housewife, was first tested in 1937 at the age of 69. She had a history of rheumatic fever in childhood and a murmur suggestive of mitral stenosis could be heard when she lay on her left side, according to her cardiac consultant; many examiners had failed to hear it. About three years before this test, under great mental strain during the last illness of her husband, she had her first transient attack of auricular fibrillation and she continued to have these attacks, usually of only a few hours duration, at occasional intervals. Despite this, when in normal rhythm, she was extremely strong and active for her years and had far less shortness of breath on exertion than most younger people. The first ballistocardiogram taken during normal sinus rhythm in 1937 was of small amplitude but otherwise normal in form. The blood pressure was 120/70.

During the interval her general health has continued excellent, although the attacks of auricular fibrillation continued. Eventually, probably about two years ago, she went into permanent auricular fibrillation. She has never been in congestive failure. At present, aged 84, she is taking digitalis and still has no undue shortness of breath, but she is definitely slowing up both mentally and physically. The ballistocardiogram taken in 1951 shows no complexes that are normal in form.

In these two cases both health and ballistocardiograms are plainly deteriorating.

In contrast are the history and records of E. N. (fig. 2) who, when aged 63, had the ballistocardiogram of a much younger person. His good health has continued; at 75 his record does show changes of the aging heart type, the I waves are smaller and the K waves deeper than when he was younger. At present he prides himself on walking between five and six miles every day, and certainly both his vigor and his ballistocardiogram are those of a much younger man.

III. *Patients Developing Ill Health of a Doubtful Character*

Case P. E., a carpenter, had no complaints when his first ballistocardiogram was taken at the age of 50. He had, however, suffered from an attack of pain of an indefinite sort for which the diagnosis of cardiac infarction was considered but abandoned after electrocardiographic studies were negative. His ballistocardiogram was altogether normal. His blood pressure was 130/80. Both ballistocardiograms are shown in figure 1.

When tested in 1950 he was 63 years old and his ballistocardiogram had deteriorated in an alarming fashion. Although the pulse rates in the two tests were very similar, 58 and 63, the size of the complexes had diminished greatly, the I and J waves of the larger complexes being 4 and 5 mm. smaller, the J wave of the small complex 5 mm. smaller than in the old record. At this time his blood pressure was 165/85.

Dr. Francis Wood examined this patient for us in ignorance of the ballistic findings, and refused to pass him as completely healthy. The blood pressure he obtained during his examination was higher than that we found after a 15 minute rest period on the ballistocardiograph, and he was impressed with the fact that the subject, an important hospital man-

tenance man well known to all of us, appeared to lack vigor and to move slowly and guardedly as one watched him at his work. But no other positive objective evidence of cardiovascular abnormality was discovered. Needless to say, the course of this subject will be followed with great interest.

Two other persons in our series have also developed ill health of a doubtful character together with a marked deterioration of their ballistocardiograms. We have decided to await developments before reporting their cases in detail.

IV. *Subjects Developing Hypertension*

Subject N. O., a teacher, had suffered from pulmonary tuberculosis as a young man. Under appropriate treatment it was completely arrested, and activity has never recurred. He has learned to lead a life appropriate to this condition, taking no strenuous exercise, and much more rest than the average person. He considered himself in excellent condition when first tested in 1937 at the age of 48. His blood pressure at that time was 120/88. This ballistocardiogram shown in figure 1 attracted attention at once because, while the waves were all normal in form, the aplitude was so small. Indeed, for his age and weight, it was one of the very smallest records we had encountered in a healthy person up to that time.

During the interval he has continued in good health, and aside from some dizzy spells, still thinks of himself as in excellent condition. However, when tested in 1951 at the age of 62, there had been a marked change in the ballistocardiogram (fig. 1), the H wave being preceded by an unusually deep G wave, while the I wave never reached the base line. No normal complexes were seen. The blood pressure was 165/110 at the end of his 15 minute rest period, so he now has a definite hypertension.

This experience is interesting from two points of view. In the first place, here is a subject with an unusually small ballistocardiogram who has developed hypertension rather than coronary disease as so many of these cases do. And second, at the time of the first test, the cardiac output, as calculated from the ballistocardiogram, was unusually low; so, to maintain the normal blood pressure then found, he must have had increased peripheral resistance at that time. The thought that people might develop the abnormality of hypertension, increased peripheral resistance, before the blood pressure rises is a challenging one.

Subject I. H., a physician, was unusually strong and vigorous when tested in 1937 at the age of 25. At this test his blood pressure was 138/85. In the interval, several years ago, hypertension was discovered. He is completely without symptoms and continues to practice very actively. At the time of his ballistocardiogram in 1951 his blood pressure was 200/120. Both these records have been illustrated in figure 2, where it will be seen at once that there has been a great diminution of the size of the I waves in the interval. No one in the healthy series suffered such a large I wave change as occurred in this patient. At the age of 39 he has a record which looks like that of an elderly man.

The records of *Subject S. J.* are also illustrated in figure 2, and they are of interest as a continuation of the story of hypertension. S. J. was completely asymptomatic when he came to be tested in 1941 at the age of 63, and he was ignorant that his blood pressure was elevated (180/100). At that time his ballistocardiogram showed an abnormally short I wave, a deep K, and indeed it looks very much like the second record of I. H.

Unfortunately, during the 10-year interval, S. J. has become completely incapacitated. He has been in congestive failure three times and when tested in 1950 was in auricular fibrillation and receiving both digitalis and mercurial diuretics. The illustration in figure 2 showing only a large and small complex does not give a fair idea of the abnormality of his record, for the largest complexes of the respiratory cycles were the only ones which could be passed as normal. The intermediate ones resembled the small complexes illustrated and the ratios of normal to abnormal complexes throughout the record was 1 to 5.

By combining the experience in the last two cases one may anticipate the changes in the ballistocardiograms which might occur as the hypertensive syndrome advances for a period of 20 years.

V. *Subjects Developing Coronary Heart Disease*

Subject F. E., a maiden lady of 59 when first examined in 1938, considered herself to be in excellent health. However, her ballistocardiogram was definitely abnormal, every J wave showing two peaks about 0.08 second apart. Her blood pressure at that time was 160/85.

During the 12-year interval she has developed angina pectoris. The onset is rather hard to date but during the past year she has had typical attacks on only moderate exertion, such as rapid climbing of one flight of stairs. Her doctor writes that an x-ray film shows the heart to be normal in size, that the electrocardiogram is essentially normal, and that the patient is taking nitroglycerin occasionally to relieve her attacks. Interestingly enough the recent ballistocardiogram does not show the split J wave which was such a prominent feature of the first record; but only an occasional complex was normal, the I wave being absent or shallow in the majority. The blood pressure is now 180/100.

This patient was not included in our first and second follow-up series on healthy persons because her blood pressure was elevated at the first test. But she evidently belongs to the ever growing group of patients whose ballistic abnormality preceded the clinical picture of coronary heart disease.

Subject S. C. has been mentioned before.[8] Secured in 1937 when the subject was 44 years old, the ballistocardiogram was entirely normal in form and larger than was to be expected from the subject's age and weight. Indeed, with a pulse rate of 81 and a blood pressure of 120/80, the calculated cardiac output exceeded the young adult mean by 20 per cent, a value exceeded by only one subject in his age group.

During the interval this subject had several attacks which might well have been angina pectoris after very unusual exertion, as was described.[8] This experience was recorded as the most divergent black dot in figure 2 of the previous report,[8] indicating a subject who, contrary to the general experience, had developed evidence of coronary heart disease despite a large ballistocardiogram of normal form.

Since that report the subject has had no more attacks suggestive of angina pectoris, and has continued to work very actively. However the ballistocardiogram taken in 1951 shows more diminution in size than any other in our series. At a pulse rate of 54 and a blood pressure of 135/79 the I and J waves of the large complexes have diminished by 2 and 6 mm. in altitude; in the small complexes they have diminished 1 and 4 mm. respectively. When the time-amplitude estimate of cardiac output used in the preceding paper[8] is employed, using the subject's actual weight, the deviation from the young adult mean is now −44 per cent. So the findings on this patient which diverged from the rest of the data in 1937 now conform with them. If a black dot to represent the present findings is placed on figure 2 of the previous paper,[8] it now appears among the other black dots.

One wonders if the high finding of 1937 could have been due to excitement, despite normal pulse rate and blood pressures. In making experiments on normal subjects the senior author has seen many instances in which increased cardiac output attributed to excitement has manifested itself without conspicuous changes in pulse rate or blood pressure. The fact that errors of this kind can creep into ballistocardiographic work, despite the painless and unalarming nature of the test, must always be kept in mind.

Subject H. C. B., a distinguished physiologist, was in excellent health when first tested in 1937 when aged 52. Indeed he was a person of unusual vigor and took great interest in performing physiologic experiments, often very rigorous ones, on himself. He had long been aware that there was a prolonged P-R interval on his electrocardiogram. His ballistocardiogram at this time was altogether normal.

An utterly fearless person, during the war he supervised and conducted research in aviation medicine and was especially concerned with the construction and testing of equipment to make it possible to live and fly a plane at extreme altitudes. On one occasion the senior author (outside the chamber) collaborated in testing equipment which permitted us to get H. C. B., alone in the chamber, up to a simulated altitude of 52,000 feet, which was the limit of the motor's power, an experiment which alarmed the senior author but not the subject. This experiment was concluded without untoward incident, but the number of times H. C. B. had blacked out in less successful experiments was very great, and I mention this in tribute to a courageous and self-sacrificing man, who never spared himself when the interests of others were concerned.

In 1948 when exercise tests were being conducted in this laboratory by Dr. Makinson,[9] H. C. B. was tested both before and after exercise. The resting record was altogether normal, but after exercise there was slurring of the J wave in the smaller complexes in records taken 10, 60, 100, 135, and 175 seconds after exercise had been completed. That taken 245 seconds after exercise was normal once more. The subject did not experience any distress whatsoever during the performance of the test. His health at this time was excellent.

In the summer of 1949 in very hot weather during a scientific meeting, he challenged several much younger colleagues to a race at underwater swimming in the hotel pool, a sport in which he was most interested and extremely proficient. He won the race easily. But that night he had an attack of precordial pain, which he suspected was due to coronary occlusion. Nevertheless, next day he started to drive his car from Atlanta to Philadelphia. On his arrival the electrocardiogram showed changes in the T wave which had not been present before, and sedimentation rate was increased, so he was admitted to the University Hospital.

His symptoms were never severe and, after a short period, both the electrocardiogram and sedimentation rate returned to their previous states and recovery seemed to be complete. He was judged to have had a minimal myocardial lesion.

Though he had pain of an indefinite character at intervals, he worked hard all the next winter. A ballistocardiogram taken at rest at this time was altogether normal and indistinguishable from the earlier records. He was not tested after exercise.

In July, 1951, planning to attend the International Physiological Congress, he had some indefinite pain in his upper abdomen just before leaving which both he and his physician thought might well be indigestion and, as his electrocardiogram was unchanged, he decided to sail. Several days later he was found dead in the bathroom of the trans-Atlantic liner.

This case is cited as our most conspicuous example of a failure to detect abnormality in a subject who died a sudden and almost certainly a cardiac death, by ballistocardiograms taken at rest. Both symptoms and electrocardiographic changes suggested that the lesion was minimal, and it is to

be noted that a test made after exercise brought out an abnormality in the ballistocardiogram.

Subject T. I. was a teacher who believed himself to be in good health when first tested in 1937 at the age of 50. A person of high emotional tension, he had difficulty relaxing during the test and the slight elevation of blood pressure found, 160/90, was attributed (rightly) to this, because hypertension did not persist. The ballistocardiogram taken at this time (fig. 2) attracted attention because of its unusually small size for his age and weight, his cardiac output, referred to ideal weight, being estimated as −38 per cent below the healthy young adult mean.[8] At the time of our first follow-up study[8] he was still in good health.

Unfortunately he suffered from a severe attack of cardiac infarction in 1949 at the age of 62 and was for many weeks in the University Hospital. A ballistocardiogram taken about six weeks after the infarction showed the bizarre complexes illustrated in figure 2, where one should note not only the very high H wave common in coronary cases, but also the large I and J waves, which are most unusual in this condition. Convalescence was slow and difficult, and he suffered from severe attacks of breathlessness for some months. It was over a year before he attempted to return to work, and after working at half pace for several months, the onset of congestive failure forced him to come to the hospital in February, 1951. Rapid improvement followed the use of mercurial diuretics and just before discharge he gave the last ballistocardiogram shown under his initials in figure 2. No normal complexes were seen.

Placed on digitalis and mercurials regularly, he improved until he was able to do light work, but in early summer he developed severe congestive failure despite therapy. He came to the hospital with marked pulmonary congestion, hemoptysis, marked hepatic enlargement, and edema of the legs as the predominating symptoms. He died suddenly next morning.

At necropsy the heart showed hypertrophy and dilatation, and there was a large infarct involving the apex and the lower part of the anterior wall of the left ventricle. The sections showed evidence of both a healed and an acute lesion. Both coronary arteries contained numerous atheromations and calcified plaques, which practically occluded the left anterior descending branch. The lungs showed a massive infarct of the right lower lobe and passive congestion. The kidneys showed mild benign nephrosclerosis; the liver and spleen, passive congestion. The thyroid was nodular but not enlarged. There was marked atherosclerosis of the aorta and other arteries.

In this case the ominous nature of the first ballistocardiogram was borne out by subsequent events, and after the first infarction neither the ballistocardiogram nor his health ever approached normal.

Discussion

The average effect of aging on the ballistocardiogram is shown in the lowest row of figure 2, where average complexes for each decade have been placed. The difference between the records of most healthy young and healthy old people can be recognized at a glance; in the "young" ballistocardiogram the two conspicuous downward points, I and K, are approximately equal in size, while in the "old" record I is conspicuously shorter than K. Comparison of the initial ballistocardiograms of subject L. G., aged 33, and subject P. E., aged 50, in figure 1 shows this difference clearly. If one knows that the subject is healthy one can make a fair guess as to his age by inspecting his ballistocardiogram.

Measurements show that as age advances, the average I wave slowly diminishes in size until, in records secured in subjects in their 60's, it is less than half the depth found in records obtained on subjects in their 20's. The average J wave diminishes also as age advances, but at a slower rate; in subjects in the 60's it is 62 per cent of the height found in subjects in the 20's. The altitude of the average H wave, the depth of K, and the duration of all the waves do not change significantly as age advances.

We believe that the physiologic implications of the changes in the ballistocardiogram which occur on aging are thoroughly understood from the results of experiments in which cardiac action was simulated in cadavers.[6] The meaning of the change in the I wave characteristic of aging is illustrated in figure 2. To produce a deep I wave experimentally the blood leaving the heart must be rapidly accelerated early in systole, and to do this requires strength. A shallow I wave and a smaller J wave occur when there is little early acceleration of "blood"; and to produce this less strength is required. So our results show that as the heart grows older it lifts its load more slowly.

In healthy young persons these changes take place slowly; those found in a 10-year period are not significant in our data. But this very slowness of change is an important fact; it means that if a rapid change occurs in any subject's ballistocardiogram it should not be

attributed to natural causes; disease should be suspected if no obvious physiologic or pharmacologic cause is found.

In healthy persons over 50 years of age when first tested, these changes take place more rapidly. In most subjects they are qualitatively identical with those of younger persons, diminution of the depth of the I and height of the J waves, but in some a further change of contour has occurred, the I wave being displaced upward until its lowest point fails to reach the base line, a form long judged abnormal because it has never been seen in healthy young adults. This abnormality has not been found in any healthy person of our series under 60 years of age, but most of those showing it give every appearance of health commensurate with their years and, in several cases, a complete cardiologic examination by Dr. Francis C. Wood disclosed nothing abnormal. Needless to say, these cases will be followed with much interest.

As disease begins and advances the changes in the ballistic contour which may develop are many and varied, but in addition to other abnormalities, diminution of the I wave, far beyond that expected for the patient's age, is a very frequent finding, and if the blood pressure has remained the same, we have a right to believe that these hearts have weakened. Diminution of the I wave may be the sole finding, as in the case of F. N. of figure 2, but in many subjects other abnormalities of contour are also evident. One of the cases described (D. N. S.) has now provided direct evidence for what was previously a belief, that, as disease or age advances, ballistic abnormalities first appear in the smallest complexes of the respiratory cycle, and then as if by spreading to the adjacent small complexes, involve increasingly large proportions of the record, the largest complexes being spared until last. So our data support the view that when the heart begins to weaken it does not contract with normal strength in that part of the respiratory cycle in which it is least well filled, a conception in accord with Starling's law. When searching for the first manifestation of cardiac weakness in any case one should scrutinize the smallest complexes of the ballistic record.

Indeed the experience described in this paper leads us to suggest a new conception. Evidence of the kind illustrated in that part of figure 2 entitled "Meaning of the Change in Form as Age Advances" has led us to believe that the heart weakening from age or disease has a recourse open to it that has not been realized. By changing the manner of systolic ejection of blood so that acceleration is kept at a minimum, the load of the heart is lifted more slowly, and by this means a heart lacking in strength can secure the greatest cardiac output possible to it, and so perhaps maintain its cardiac output unimpaired. However, this change in cardiac function can be detected by the change in the form of the ballistocardiogram, and since this adaptation may permit the heart's function, that of pumping blood, to remain essentially unimpaired, we see a reasonable explanation for the observation that the ballistic record can detect myocardial abnormality very early in the course of disease, and may detect it before the development of symptoms or of other clinical evidence of myocardial dysfunction.

That changes in the ballistic record of resting subjects do not always precede the onset of serious cardiac disease should surprise no one; in our experience with H. C. B. we have reported a conspicuous example of such a failure. Certainly such failures should be expected in any lesion too small to cause a detectable diminution of the strength of the cardiac contraction, but such a small lesion still might kill by inciting fibrillation of the ventricles. Doubtless ballistocardiograms taken routinely after exercise will increase our ability to detect cardiac abnormality, as was the case in this instance. All our methods are still in their infancy and the search for both better instruments and better ways of using ballistocardiograms must be actively continued.

In conclusion, as an answer to many questions from practicing physicians, let us give a brief statement of our idea of the place of the ballistocardiogram among the other clinical methods. Giving information about the motion of the blood, its data, combined with knowledge of blood pressure, are related to the power of the heart, but the best method of combining the two to get a useful single numerical value

is still in doubt. The relationship between the ballistocardiogram and the electrocardiogram can be vividly presented to most readers by rough analogy to the gasoline engine. The electrocardiogram gives information about the spark, the ballistocardiogram about the explosion. Abnormality of one is often associated with abnormality of the other, but this is by no means always true. The utility of the ballistocardiogram stems from the fact that it contributes so much to our knowledge of the heart's "explosion."

Summary and Conclusions

1. Second ballistocardiograms have been secured on a group of 80 subjects who, as part of the normal standard series, had undergone this test from 10 to 14 years before.

2. In this 10- to 14-year interval 65 of these subjects continued in good health. The records of these subjects have provided normal standards for the size and duration of the major ballistic waves. The changes during the interval have allowed us to estimate the effect of aging on the ballistic record. The principal effect is a steady diminution in depth of the I wave, with a lesser diminution of the J wave.

3. Our physiologic interpretation of this change of ballistic form is that, as age advances, the heart lifts its load more slowly. By such an adaptation a normal cardiac output could be maintained for a time by a heart whose power was diminishing, and a weak heart could secure the maximum cardiac output possible to it.

4. In the same interval 15 of our subjects have lost their health. The clinical histories of most of these patients are given in detail and the relations between their illnesses and the changes occurring in their ballistic records have been discussed.

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The Tissue Distribution and Excretion of Radioactive Digitoxin

Studies on Normal Rats and Cats, and Rats with Dietary-Induced Myocardial Lesions

By C. S. Fischer, A. Sjoerdsma and R. Johnson

The tissue distribution and excretion of radioactive digitoxin and its metabolites were studied in normal rats and cats and in rats with dietary induced myocardial lesions. The prolonged cardiac and renal retention of digitoxin and its derivatives, associated with the persistence of these substances in the excreta of sensitive animals, supports the concept of storage as an explanation for the cumulative action of certain of the cardiac glycosides. There is a suggestive increase in digitoxin metabolism in heart failure.

RECENT publications[1-3] from this department have demonstrated the feasibility of studying the fate of C^{14}-labeled digitoxin in the experimental animal. The extreme sensitivity of this tracer technic permits the use of sublethal doses and offers, in addition, the advantage of accurate evaluation of the derivatives of digitoxin metabolism in samples of tissue or excreta. Previous preliminary studies[2] suggested that the unaltered glycoside and its metabolites quickly appeared in body organs and the excreta following the parenteral administration of the radioactive drug. The rapidity with which the intermediary metabolism and excretion occurred was interpreted as casting doubt on the conventional storage theory of cumulative action. On the other hand the authors[3] have recently shown that the isolated hearts of various animals differ in their ability to fix radioactive digitoxin and its metabolites and to maintain this fixation during washing. Other investigators, making use of biologic technics, have noted similar phenomena but were handicapped by either the insensitivity of their technics or the inability to evaluate the metabolic derivatives of the glycosides.

Having established the ability of the isotope technic to encompass both the problems of sensitivity and metabolites in biologic media, it was decided to extend the investigation of the fate of digitoxin in the intact animal. For this purpose we chose a very resistant animal, the rat, and a relatively sensitive animal, the cat. Included in this study were rats with myocardial lesions, it being our belief that further information might be gained from a similar investigation in such preparations.

Methods

Sixteen animals were used in these experiments: (1) four normal rats with an average weight of 340 Gm., (2) four normal cats each weighing about 2.5 Kg., and (3) eight rats with a syndrome resembling congestive heart failure weighing approximately 160 Gm. each. Myocardial lesions characteristic of potassium deficiency were induced in the latter animals by Dr. Paul Cannon and associates of the Department of Pathology using a method recently described by them.[4] In this method, albino rats are fed a protein-deficient diet for approximately two and one-half to three months, followed by a diet adequate in amino acids, calories and in all electrolytes except potassium. After about two weeks on the latter regime, the animals develop myocardial lesions and shortly thereafter exhibit signs suggestive of congestive heart failure, including cardiac dilatation, pulmonary edema and passive congestion of the liver. Death supervenes shortly if the deficient diet is continued. Three of the eight rats in

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the group were not given digitoxin but were subjected to pathologic examination which confirmed the presence of the characteristic lesions described. The other five were each given 50 μg. of radioactive digitoxin in 0.5 cc. of 40 per cent ethanol by tail vein. The four normal rats were injected similarly, while the four cats were each given 125 μg. of radioactive digitoxin in 1.5 cc. of 40 per cent ethanol. The cats were under light ether anesthesia at the time of injection into a vein on the forelimb. The animals were placed in metabolism cages and their urine and feces collected for the duration of the experiment. At 1 hour, 6 hours, 24 hours, 3 days and 1 week after injection, animals were sacrificed in the preprandial state and all the major organs analyzed for digitoxin and its metabolites.

Except for slight modifications, the analyses were carried out by the method described previously.[3] For study, urine was used either undiluted or diluted to sufficient volume for extraction, stools were made into 5 per cent homogenates in distilled water, while 10 per cent homogenates were made of all the major organs. One cc. aliquots were plated in duplicate on flat copper discs for measurement of total radioactivity. Unchanged digitoxin was extracted from 5 to 10 cc. aliquots of the same specimens. Following extraction of each sample with chloroform containing a small amount of nonradioactive digitoxin, the solution was added to a 5 × 120 mm. adsorption column containing reactivated alumina. Elution was then carried out in turn with 1 per cent and 10 per cent ethanol in chloroform. Unchanged digitoxin resides in the latter fraction. The columns could be washed free of residual radioactivity by successive elution with 95 per cent and 50 per cent ethanol. The amount of activity remaining in the column was found in all cases to be quantitatively identical to control studies in which known amounts of radioactive digitoxin were added to the various mediums and then carried through the extraction process. For counting, dried residues of the fractions were transferred to copper cups by dissolving in 1 cc. of 10 per cent ethanol in chloroform and the beakers were washed twice with 1 cc. of 50 per cent ethanol. All plated material was dried under a warm blower. In some cases, 1 cc. aliquots of water-soluble residues remaining after chloroform extraction were also plated. The samples were counted in internal open window Geiger counters.[8]

The radioactive digitoxin used had an average specific activity of 462 counts per minute per microgram. Specific absorption correction factors were prepared for tissue homogenates, urine, bile and feces and corrections applied when indicated. In control in vitro experiments the recovery of digitoxin from body tissues and fluids was about 70 per cent. Complete recovery is always limited by hydrolysis and a small but significant adsorption to glassware, particularly with the minute amounts employed in this study. By virtue of the fact that a larger aliquot is taken for extraction, the sensitivity of the method for digitoxin is greater than for metabolites.

Results

Figure 1 is a graphic presentation of the daily excretion of carbon-14–containing substances after the intravenous administration of radioactive digitoxin. The total carbon-14 values were calculated from direct counts on stool homogenate and urine, while the figures for digitoxin excretion represent extraction values. Total carbon-14 is equal to the sum of digitoxin and its metabolic derivatives. Both the cat and rat rapidly eliminated digitoxin and metabolites but the rat seemed to do so more quickly. The rat excreted about 75 per cent of the total injected dose within two days, while a similar amount was recovered only after three to four days from the cat. Although excretion was virtually complete after seven days, small amounts of these substances could still be detected in the urine and feces of both animals. The excretion rate of unchanged digitoxin followed the same general pattern. The results of similar experiments on potassium-protein deficient rats with a syndrome resembling congestive heart failure are given in figure 2. These results show that there is no striking deviation from the normal.

Excretory data on one rat, one cat, and the average of two deficient rats is shown in table 1, with separate recordings for urine and feces. Only 5 per cent of the total urinary excretion of carbon-14 by the cat consisted of digitoxin. This contrasts with about 30 per cent for the normal rat. The deficient rats more nearly resembled the cat, with 12 per cent of the radioactivity in the urine accounted for as digitoxin. The activity of the feces did not differ remarkably in the three groups with respect to its partition between unchanged digitoxin and digitoxin derivatives. Digitoxin constituted about 25, 35 and 25 per cent of the fecal excretion for cat, rat and deficient rat, respectively. However, in successive days a consistent finding in both urine and feces of all animals was the tendency for the digitoxin–total carbon-14 ratio to decrease, while the water soluble fraction increased. A distinct variation between the animals exists when one considers the relative

TABLE 1.—*Excretion of Digitoxin and Its Derivatives by Normal and Deficient Animals*[a]

Day	Normal Cat[e]			Normal Rat[b]			Deficient Rats[b]		
	Urine – 55%[c]			Urine – 30%[c]			Urine – 12%[c]		
	Digitoxin	Metabolites	% Digitoxin[d]	Digitoxin	Metabolites	% Digitoxin[d]	Digitoxin	Metabolites	% Digitoxin[d]
1	1.36	10.84	11	2.89	4.71	38	0.58	4.02	13
2	0.49	13.51	4	1.20	1.65	42	0.09	0.63	12
3	0.26	3.75	6	0.11	0.66	14	0.03	0.45	6
4	0.86	12.94	6	0.03	0.66	4	0.02	0.26	7
5	0.24	10.46	2	0.01	0.87	1	—	—	—
6	0.15	4.50	3	trace	0.88	—	—	—	—
7	0.14	7.54	2	trace	0.94	—	—	—	—
Total	3.50	63.63	5	4.24	10.37	29	0.72	5.36	12
Day	Feces – 45%[c]			Feces – 70%[c]			Feces – 88%[c]		
	Digitoxin	Metabolites	% Digitoxin[d]	Digitoxin	Metabolites	% Digitoxin[d]	Digitoxin	Metabolites	% Digitoxin[d]
1	3.96	10.54	27	5.23	8.57	38	1.83	3.90	32
2	4.18	9.42	31	4.77	9.83	33	6.25	16.17	28
3	4.98	15.72	24	1.76	3.48	34	1.76	4.68	26
4	0.78	2.74	22	0.28	1.17	19	1.27	4.83	21
5	0.38	2.82	12	0.14	—	—	0.62	2.98	17
6	trace	—	—	0.08	0.40	17	0.14	0.92	13
7	trace	—	—	trace	trace	—	0.08	0.64	11
Total	14.28	41.24	26	12.26	23.45	34	11.95	34.12	26

[a] Digitoxin and metabolites are expressed as μg. equivalents of digitoxin.
[b] Given 50 μg. of radioactive digitoxin intravenously.
[c] Percentage of total excretion by this route.
[d] Percentage of C^{14} attributable to unchanged digitoxin.
[e] Given 125 μg. of radioactive digitoxin intravenously.

magnitudes of urinary and fecal excretion. In the cat, the total seven day excretion was about equally divided between urine and feces. However, in rats the predominant excretion was by the intestinal route, being 70 and 88 per cent of the total for normal and deficient rats, respectively.

The results of the distribution studies are shown in tables 2, 3 and 4. Since five times as much tissue was extracted as was counted directly, it is not surprising that in some cases digitoxin was recovered where no significant activity was detectable in the direct counts (digitoxin plus metabolites). The studies on normal rats show that within one hour, 8.3 μg. of the injected material was concentrated in the liver, and 3.6 μg. had already passed into the small intestine where only 12 per cent was found to be digitoxin. The concentration of digitoxin in the heart and kidney was about twice that in skeletal muscle, while the concentration in the liver was 15 times as great. After six hours there was a decided increase in the radioactivity of the small intestine and contents while the colon now contained 11. 2 μg., 34 per cent of which was digitoxin. This excretion in the intestinal tract was accompanied by a marked fall in tissue levels other than the liver. In 24 hours, about 21 μg. was still present in the animal, but except for 0.35 μg. of metabolites found in the lungs, all of the drug was concentrated in the liver and intestinal tract. The total radioactivity in the liver had fallen to 3.2 μg. and the digitoxin percentage had dropped to 10 per cent. It should be noted that in passage down the intestinal tract the percentage of digitoxin had increased significantly, the percentage for colon being consistently higher than for small intestine, suggesting the excretion of digitoxin by the colon. After seven days, the only activity in the rat was a trace of digitoxin in the colon.

The cats, which received only one-third as much digitoxin on a weight basis as the rats, showed marked and prolonged concentration of the drug in the heart and kidney, in addition to the hepatointestinal pattern seen in the rat. Radioactivity amounting to 5.2 μg. was recovered from the kidney after one hour 3.2 μg. after 24 hours, 2.83 μg. after three days and 0.62 μg. after one week. The percentage of digitoxin in the kidney was also remarkably high. The concentration of radioactivity in the heart (0.27 μg. per Gm.) at one hour was exceeded only by that in the kidney (0.39 μg. per Gm.) and was at least 20 times as great as skeletal muscle. The cardiac digitoxin percentage at one hour and 24 hours (26 per cent and 10 per cent) in contrast to the much higher percentage in the kidney suggests a retention of digitoxin by the kidney and a production and utilization of metabolites by the heart. Another striking finding was the very large amount of radioactivity in the bile, its persistence there, and its low digitoxin percentage. Direct comparison with the rat is not possible because of the absence of a gall bladder in this animal. After seven days, the only measurable radioactivity in the cat was digitoxin in the kidney and metabolites in the bile.

Deficient rats displayed only minor differences from normal rats. At one hour the heart seemed to show an increased affinity for the drug with a concentration five times that of skeletal muscle, but no measurable amount remained after six hours. Radioactivity persisted in the kidneys (0.38 μg.) for at least six hours, but in marked contrast to the cat, only 16 per cent was digitoxin. Metabolites were again found in the lungs after 24 hours. As in normal rats and cats, the digitoxin percentage increased during passage through the intestine.

Discussion

Our studies on the excretion of digitoxin are in complete agreement with the previously held concept that this drug is excreted slowly over a period of days or weeks but we are only in partial agreement with the rate at which this elimination occurs. According to Weese[6] and Hatcher[7] digitoxin is utilized to the extent of 4 to 5 per cent a day and consequently this amount appears daily in the combined excreta either as unchanged digitoxin or its derivatives. Friedman and Bine,[8] on the other hand, have observed a somewhat more rapid rate of urinary excretion of unchanged digitoxin in rats, a finding approximately equal to our own. However, utilization of the isotope technic has enabled us to establish the concomitant pres-

TABLE 2.—*Tissue Distribution of Digitoxin and Metabolites in Normal Rats*
50 μg. of Radioactive Digitoxin Given Intravenously

Organ[a] or Tissue	One Hour					Six Hours					24 Hours					Seven Days
	Digitoxin		Metabolites		Digitoxin %	Digitoxin		Metabolites		Digitoxin %	Digitoxin		Metabolites		Digitoxin %	
	μg./Gm.	total μg.	μg./Gm.	total μg.		μg./Gm.	total μg.	μg./Gm.	total μg.		μg./Gm.	total μg.	μg./Gm.	total μg.		
Heart	0.07	0.06	trace	—	—	0.04	0.04	trace	trace	—	I	—	I	—	—	Except for trace in colon no detectable radioactivity in any organ or tissue
Liver	0.62	5.40	0.33	2.90	65	0.32	3.08	0.24	2.30	57	0.04	0.32	0.33	2.88	10	
Kidney	0.08	0.16	0.02	0.04	82	0.03	0.06	I	—	—	I	—	I	—	—	
Lung	0.06	0.05	I[c]	—	—	trace	—	trace	—	—	I	—	0.22	0.35	—	
Stomach[b]	I	—	0.28	0.50	—	0.03	0.05	0.24	0.39	11	I	—	I	—	—	
Small intestine[b]	0.06	0.43	0.48	3.17	12	0.24	1.83	0.70	5.18	26	0.01	0.04	0.64	4.36	1	
Colon[b]	I	—	I	—	—	0.75	3.76	1.48	7.45	34	0.57	2.38	2.62	10.82	18	
Muscle	0.04	—	trace	—	—	0.02	—	I	—	—	I	—	I	—	—	

[a] Brain of 24 hour animal contained 0.29 μg. metabolites; spleen was nonradioactive in all cases. [b] And contents. [c] I = insignificant counts.

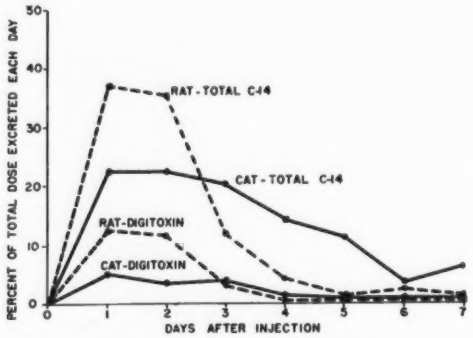


FIG. 1. The daily excretion of digitoxin and its metabolites by normal rats and cats. Fifty μg. of radioactive digitoxin were administered intravenously to rats, 125 μg. to cats.

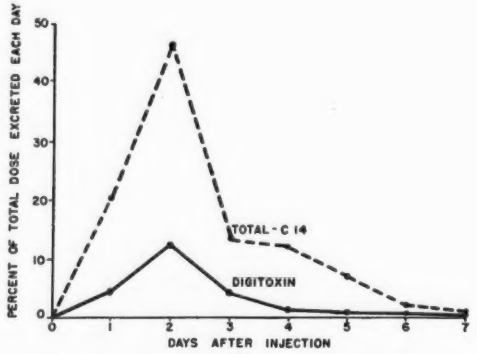


FIG. 2. Excretion of digitoxin and metabolites by potassium-protein deficient rats with myocardial lesions. Fifty μg. of radioactive digitoxin were administered intravenously. Each point is an average of data obtained on two rats, which were studied for a seven day period.

ence of metabolic derivatives in the urine. The importance of this observation is emphasized by the fact that although unaltered digitoxin is found in the urine to the extent of only 5 per cent on any given day, the total derivatives constitute over three times this amount. Evaluation of digitoxin and its metabolites in the feces of experimental animals has not been achieved using the chemical and biologic methods hitherto available. With the isotope technic, findings analogous to the urine results were obtained. If both urine and feces are considered, the total excretion represents 20 to 40 per cent of the administered dose on the first day with decreasing amounts thereafter. While the concept of slow excretion of digitoxin as such was a valid one, its quantitative aspects were therefore either erroneous or misleading, since no estimations of the metabolic derivatives were given.

Measuring the tissue distribution of digitoxin in the intact animal presented even greater difficulties to previous workers. The employment of huge and sometimes lethal doses gave variable results but the early conclusions of Hatcher indicated no predilection for any particular organ. Later, Hatcher and Eggleston indirectly demonstrated that the liver was an organ of digitoxin destruction. The major role played by the liver in digitoxin metabolism in both the rat and cat has been clearly indicated by our own and previous studies from this department using the labeled glycoside.

A major difference between the two species of animals was the persistence of digitoxin and its metabolites in the cat heart and the absence of significant fixation in the rat heart. Although this same problem of digitoxin binding by heart muscle was dealt with in previous reports on isolated hearts by Sjoerdsma and Fischer,[3] and by Geiling,[10] the present studies on intact animals are in complete agreement with these experiments, and strengthen the hypothesis that persistent cardiac action is due at least in part to the presence of small amounts of the drug and its metabolites in the hearts of sensitive animals. Our finding and those of Bine and his co-workers[11] that the rat heart has little or no ability to metabolize digitoxin or retain its derivatives supports our belief that unchanged digitoxin is a requisite for the cardiotonic effect, and in acting is metabolized and detoxified into derivatives which are both water soluble and relatively inactive.

Another marked difference between the cat and the rat was the prolonged appearance of a high concentration of digitoxin in the kidney of the cat, whereas little or none was found in this organ of the rat. This finding has greater significance if it is recalled that the urine of the cat showed very little digitoxin but a high concentration of metabolites. The conclusion is that the kidney of the cat, and perhaps other sensitive animals as well, selectively excretes metabolites and retains the unchanged drug. This constitutes an economy of digitoxin for the animal and, although occurring in the presence of rapid excretion, is evidence in support of a storage theory of cumulative action and further supports the conclusion that unchanged digitoxin is essential for the cardiac effect.

Although there is a probable tissue increase in metabolites and a distinctly higher concentration of digitoxin derivatives in the urine of the deficient animals, the differences between them and normal animals do not justify any final judgment as to the action of digitoxin in heart failure. We are suggesting, however, that there may be an increased digitoxin metabolism and utilization in animals with congestive heart failure.

Summary

The tissue distribution and excretion of radioactive digitoxin and its metabolites were studied in normal rats and cats, and in rats with dietary-induced myocardial lesions. Digitoxin was reisolated from tissue and excreta by isotope dilution and selective adsorption onto alumina with ethanol and chloroform solutions, while metabolites were evaluated by direct counts of the samples.

Digitoxin is largely metabolized in the animal and is excreted chiefly as its metabolic derivatives in the normal rat and to a somewhat greater extent in the normal cat and in rats with a syndrome resembling congestive heart failure. The metabolites are predominantly water soluble, appearing in both urine and feces in this form.

TABLE 3.—*Tissue Distribution of Digitoxin and Metabolites in Normal Cats*
125 μg. of Radioactive Digitoxin Given Intravenously

Organ[a] or Tissue	One Hour					24 Hours					72 Hours					Seven Days
	Digitoxin		Metabolites		Digitoxin %	Digitoxin		Metabolites		Digitoxin %	Digitoxin		Metabolites		Digitoxin %	
	μg./Gm.	total μg.	μg./Gm.	total μg.		μg./Gm.	total μg.	μg./Gm.	total μg.		μg./Gm.	total μg.	μg./Gm.	total μg.		
Heart	0.07	0.49	0.20	1.51	26	0.04	0.33	0.34	2.97	10	0.02	0.24	I	—	—	No radioactivity detectable in any organ or tissue except the gall bladder, 0.33 μg. of total activity, and the kidney, 0.62 μg. of digitoxin
Liver	0.09	4.08	0.09	4.42	48	0.02	1.24	0.09	4.96	20	0.04	2.59	I	—	—	
Kidney	0.19	2.54	0.20	2.66	49	0.21	2.98	0.02	0.22	93	0.13	2.83	I	—	—	
Gall bladder and bile	0.06	0.17	4.90	14.23	1.2	0.53	1.06	4.43	14.14	7	0.19	0.84	1.32	5.96	12	
Stomach[b]	I[c]	—	trace	I	—	I	—	I	—	—	0.04	1.01	I	—	—	
Jejunum[b]	I	—	I	I	—	0.04	0.94	I	—	—	0.05	1.69	I	—	—	
Ileum[b]	I	—	I	I	—	0.03	0.64	0.16	3.62	15	0.06	2.28	0.39	15.19	13	
Colon	I	—	I	I	—	0.08	0.96	0.02	0.24	80	0.07	0.99	I	—	—	
Muscle	I	—	I	I	—	I	—	I	—	—	I	—	I	—	—	

[a] Spleen, lung, and brain had no significant activity. [b] And contents [c] I = insignificant counts.

TABLE 4.—*Tissue Distribution of Digitoxin and Metabolites in Potassium-Protein Deficient Rats*
125 μg. of Radioactive Digitoxin Given Intravenously

Organ[a] or Tissue	One Hour					Six Hours					24 Hours					Seven Days
	Digitoxin		Metabolites		Digitoxin %	Digitoxin		Metabolites		Digitoxin %	Digitoxin		Metabolites		Digitoxin %	
	μg./Gm.	total μg.	μg./Gm.	total μg.		μg./Gm.	total μg.	μg./Gm.	total μg.		μg./Gm.	total μg.	μg./Gm.	total μg.		
Heart	0.04	0.04	0.16	0.10	28	I	—	trace	—	—	I	—	I	—	—	No detectable radioactivity in any organ or tissue
Liver	0.84	5.67	0.36	2.45	70	0.58	3.43	0.50	2.93	54	0.03	0.17	I	—	—	
Kidney	0.11	0.22	0.09	0.17	56	0.03	0.06	0.18	0.32	16	I	—	I	—	—	
Lung	0.09	0.10	0.15	0.15	40	0.03	0.04	I	—	—	I	—	0.20	0.21	—	
Stomach[b]	0.08	0.13	—	—	—	0.10	0.21	0.21	0.46	31	0.46	1.12	0.86	3.06	35	
Small intestine[b]	0.86	3.21	2.04	7.53	30	1.31	8.60	4.77	31.39	21	0.52	2.54	1.58	7.71	25	
Colon[b]	I[c]	—	I	—	—	0.36	1.42	0.24	0.93	60	4.46	13.44	6.82	20.51	40	
Muscle	0.04	—	trace	—	—	trace	—	I	—	—	I	—	I	—	—	

[a] Spleen and brain had no significant activity. [b] And contents. [c] I = insignificant counts.

The prolonged fixation of digitoxin and its metabolites in the heart of the cat associated with the appearance of high concentrations of metabolites in the excreta suggests that unchanged glycoside may be responsible for the cardiotonic effect and that the cumulative action of digitoxin is due to the persistence of the drug and/or its derivatives in the tissues.

There is a suggestion of an increase in digitoxin metabolites in the tissues and excreta of animals with myocardial lesions and certain of the elements of congestive heart failure.

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The George Fahr Lecture

Certain Mechanical Peculiarities of the Human Cardiac Pump in Normal and Diseased States

By G. E. Burch, M.D., C. T. Ray, M.D., and J. A. Cronvich, M.S.

This is a general theoretic consideration of certain mechanical peculiarities of the human heart. It includes a discussion of mechanical advantages of the average size and average pressures, the effects of various pressures and ventricular volumes on ventricular work and "load," mechanical advantages of the structural arrangement of muscular fibers and manner of contraction, as well as the time course of ventricular work and power produced during a cardiac cycle. The role of the trabeculae carneae and papillary muscles in the emptying of a normal sized ventricle is also discussed.

ALTHOUGH some thought has been given to the peculiarities of the mechanical nature of the human heart as a pump, the importance of these functional peculiarities is usually disregarded by those who discuss the hemodynamics of the cardiovascular system. Because of these mechanical factors the normal heart tends to maintain the same "load" or may even reduce its "load" as systole progresses and the intraventricular pressure increases. On the other hand, the dilated diseased heart loses this advantage, the loss being especially significant in the presence of arterial hypertension. It is the purpose of this theoretic discussion to indicate some of these hemodynamic principles and to point out some of the differences that exist between the normal and the dilated heart. In this presentation the term "load" denotes the force that must be supported by the ventricles of the heart during the cardiac cycle. Although the left ventricle of the human heart is considered throughout this presentation, the same concepts may be applied to the right ventricle as well as to the hearts of all animals which are shaped similar to and contract like that of man.

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The Heart

The human heart is irregular in shape, but for clarity and simplicity, it will be assumed in these discussions that the intraventricular cavities are spherical. The trabeculae carneae and papillary muscles which render the intraventricular cavities irregular do not materially alter the arguments to follow. Certain problems related to these intraventricular structures are presented.

If the ventricular cavity is considered to be spherical in shape, then the area of its internal surface is (fig. 1)

$$A = 4\pi r^2$$

and its internal volume is

$$V = \frac{4}{3}\pi r^3$$

where r is the internal radius of the sphere. The ratio of the volume to the area is, therefore, $\frac{1}{3}\ r$. Thus, when the size of the sphere is altered, its volume changes more rapidly than its surface area. The heart may be considered a sphere whose size is continuously changing and, therefore, so are its internal surface area and internal volume.

The size of the left ventricle of the human heart was accepted for this discussion to vary from an average maximum internal volume of 85 cc. at the beginning of systole to an average minimum volume of 25 cc. at the end of systolic ejection.[1, 2] Associated with this change in volume is a change in internal surface area, from 93.7 to 41.2 sq. cm. It is fortunate that there is such a change in area, for the pressure

within the ventricle increases as systole progresses, for example, from essentially zero to 70 mm. Hg when the aortic valve opens or the diastolic aortic pressure is exceeded, to 120 mm. Hg when the systolic pressure is attained. Therefore, since the pressure within the ventricle and its internal surface area are changing, the force or "load" upon the internal wall may be changing also (fig. 2).

The total radial force, F, acting upon the internal wall of the ventricle is expressed by the equation

$$F = PA$$

where P is the pressure and A is the area of the wall which is supporting the radially acting pressure.

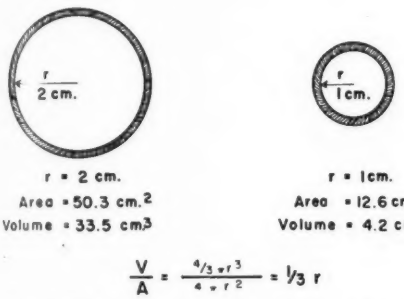


FIG. 1. Relationship of surface area and volume of a sphere.

When the left ventricle contracts, its internal area decreases but its internal pressure rises. It is, therefore, of interest and of importance to know how the force varies as systole progresses. In the average normal adult with a systolic blood pressure of 120 mm. Hg and a diastolic pressure of 70 mm. Hg, the total radial force acting upon the wall internally at the moment the aortic valve opens or when the diastolic level of arterial pressure is just exceeded would be

$$F = 70 \times 93.7 \times 1333.2 = 8.7 \times 10^6 \text{ dynes}$$

where 93.7 is the internal surface area in sq. cm. of the left ventricle filled with 85 cc. of blood in diastole and 1333.2 is the pressure in dynes per sq. cm. equivalent to a pressure of 1 mm. Hg.

When the left ventricle has completed its ejection of blood and the systolic level of pressure in the aorta has been reached, the total radial force acting upon the wall internally would be

$$F = 120 \times 41.2 \times 1333.2 = 6.6 \times 10^6 \text{ dynes}$$

where 41.2 is the internal surface area in sq. cm. of the left ventricle for a residual blood volume of 25 cc. at the end of systolic ejection.

It is interesting and surely of considerable importance that, even though the left ventricle must pump its blood against a progressively increasing pressure, once the aortic diastolic pressure has been reached and the ventricular

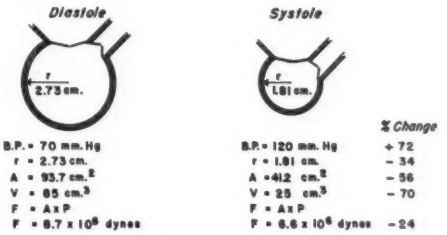


FIG. 2. Relationship of surface area, volume and load of normal left ventricle. The values shown on the left, labeled diastole, are those obtained when the aortic diastolic pressure is reached and the aortic valves open. Those shown in the right column, labeled systole, are the values obtained at the end of maximum ejection when the systolic pressure is reached. The third column indicates the direction and percentage of change of various values from the beginning to the end of ejection. The symbols are defined in the text.

volume begins to decrease as blood is ejected into the aorta, the "load" on the ventricle does not rise further but actually declines. This feature establishes a unique characteristic for the cardiac pump not possessed by reciprocating pumps employed in industry or engineering generally.

Figure 3 shows the influence of the intraventricular diastolic blood volume upon the ventricular "load." It is certainly interesting to find that for the normal heart the load does not increase during systole once it begins to eject blood. Figure 3 also shows that this advantage is lost as the ventricle dilates. When the diastolic volume becomes large, the load progressively increases as the ventricle ejects blood. For example, with a blood pressure of

120/70, from the point of view of load, it is disadvantageous for the dilated ventricle to eject blood. Figure 3 deserves careful study and consideration.

Even in the presence of hypertension, the "load" or total force exerted upon the left ventricle of a heart of normal size is not considerably different quantitatively or qualitatively from that of the subject without hypertension and a normal sized heart. For example,

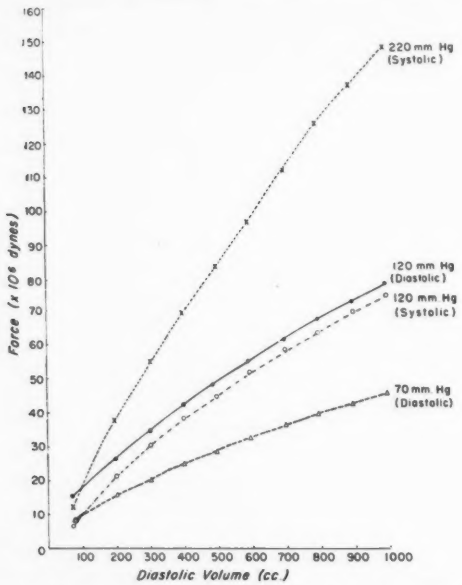


FIG. 3. Relationship of load on the left ventricle to intraventricular volume at the time the diastolic and systolic aortic pressures are reached. Volumes are plotted for blood pressure of 120/70 and of 220/120. It it assumed in this plot that there is a constant stroke volume of 60 cc.

if the volume ejected is 60 cc., the arterial systolic blood pressure is 220 mm. Hg and the diastolic 120 mm., the "load" supported by the left ventricle changes from 15.0 $\times$ 10^6 dynes, when the diastolic arterial pressure is reached and ejection of blood into the aorta begins, to 12.1 $\times$ 10^6 dynes, when the systolic pressure of 220 mm. Hg is attained (fig. 3). On the other hand, once the ventricle begins to dilate, the picture changes conspicuously (fig. 3). For example, when the diastolic volume of the left ventricle is 500 cc., the stroke output 60 cc. and the arterial blood pressure 220/120, the total force against the intraventricular wall is 48.7 $\times$ 10^6 dynes when the aortic valve opens. The load increases to 81.6 $\times$ 10^6 dynes when the 60 cc. are ejected and the systolic pressure is reached (fig. 3).

It is evident, then, that the normal left ventricle functions with essentially ideal diastolic and stroke volumes. Although left ventricular dilatation may increase the ability of the myocardium to do work according to

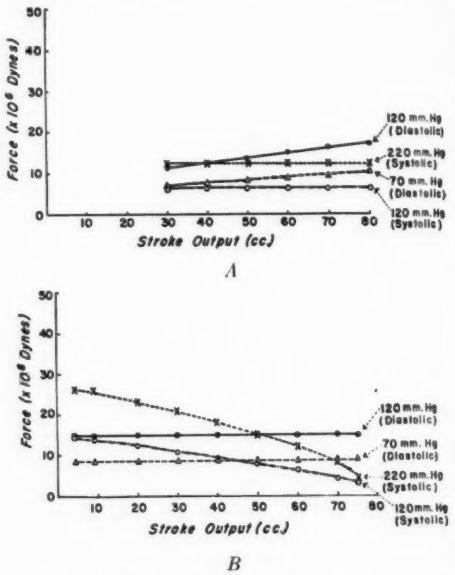


FIG. 4*A*. Relationship of volume of ventricular ejection to load. Volume at end of systole constant (25 cc.).

B. Relationship of volume of ventricular ejection to load. Diastolic volume constant (85 cc.).

Starling's law, it is also evident from figure 3 that dilatation increases the load on the left ventricle and, therefore, the "physiologic" work that the ventricle must perform per beat. The significance of this extra load and its relation to Starling's law remain to be studied.

Figure 4*A* shows the variations in load upon the left ventricle with arterial blood pressures of 120/70 and 220/120 mm. Hg, in which the stroke volume varies from 30 to 80 cc. and the intraventricular volume is 25 cc. at the end of systolic ejection. It is evident that the load

varies relatively little even though the pressures within the ventricle differ considerably.

Figure 4*B* shows the variations in load upon the left ventricle with arterial pressures of 120/70 and 220/120 mm. Hg, with the stroke volume varying from 5 to 75 cc., and with the intraventricular diastolic volume fixed at 85 cc. A decline in the systolic load is seen as the volume of the ventricle decreases at the end of systole. Figures 3, 4*A*, and 4*B* show the relative influence of changes in intraventricular volume and pressure upon ventricular load, including the disadvantageous effect of dilatation upon intraventricular loading. Because dilatation of the ventricle increases the intraventricular surface area, the total force exerted upon the ventricular wall increases.

TABLE 1.—*Energy Per Day Necessary to Overcome Left Ventricular "Load" in the Normal and Dilated Heart.*

Cardiac Rate 60

Work/Day	Normal Heart, Systolic B.P. 120	Dilated Heart (Diastolic Vol. 500 cc.)	
		Systolic B.P. 120	Systolic B.P. 220
Ergs	43.2×10^{10}	388.8×10^{10}	691.2×10^{10}
Kg. Cal.	10.37	93.6	166.4
Ft. Lb.	32,000	288,000	512,000

Useful work in the first two examples is approximately 1.5 times the values shown and 3 times the values shown in the third example.

This increase may theoretically produce detrimental overloading of the ventricle and might conceivably produce a serious irreversible physiologic cycle. A normal left ventricle, with its relatively small internal surface area and further reduction in area as it empties during systole, would not "overload." The relative advantage of dilatation, which according to Starling's law is associated with an increase in the force of contraction, and the associated disadvantage of increasing the load on the ventricle require study.

It is not possible with the data available to determine the "physiologic" work performed by the heart in association with the loads described. Obviously, no work is performed in the strict physical sense when maintaining "tone," but foodstuffs and oxygen are consumed and heat is liberated to maintain the tone of the myocardium necessary to cope with these loads. The amount of metabolism performed and the heat liberated in association with the load must vary with the load. They should be greater in the dilated heart than in the normal one. The comparative hypothetic values of the forces concerned are presented in table 1. It is assumed that if the load, represented by radial force in dynes, were made to perform work by being associated with translation of motion of 1.0 cm., the force would be converted into ergs of work. Table 1 shows a comparison of the situation if the radial forces of a normal and of a dilated heart were converted to work by acting through a distance of 1.0 cm. It is necessary to exercise caution when considering these values, as they are

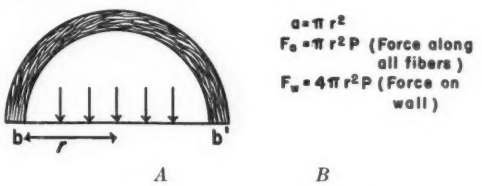


FIG. 5. This illustration shows the manner in which radial pressure and force exert a longitudinal force upon the muscle fibers of a ventricle. In this figure, *a* is the area of the diaphragm discussed in the text.

purely hypothetic and are presented only for thought.

LONGITUDINAL FORCE, LOAD, OR TENSION UPON THE CARDIAC MUSCLE FIBERS

It has been shown in the preceding discussion that the load or radial force upon the entire internal wall of the ventricle is given by the equation

$$F = 4\pi r^2 P$$

The force acting along the fibers "longitudinally" is given by the equation

$$F = \pi r^2 P$$

Therefore, the force or load applied longitudinally upon al fibers collectively of the myocardium is one-fourth that exerted laterally upon the wall (fig. 5); that is, the tensile force necessary for the muscle fibers of the ventricle to develop in order to maintain the radial

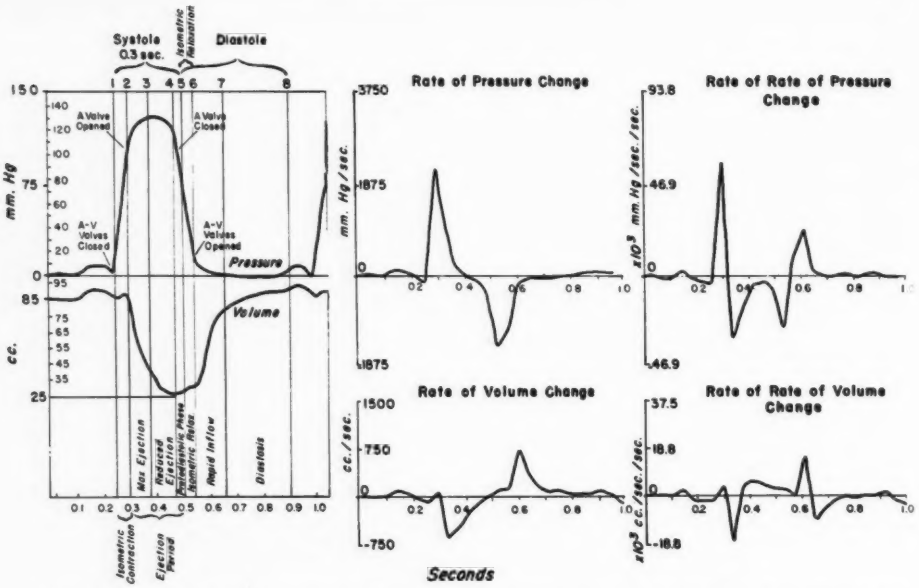


FIG. 6. Intraventricular pressure and volume of the average normal heart taken from the studies of Wiggers and his associates. The simultaneous variations with time are evident from the plots.

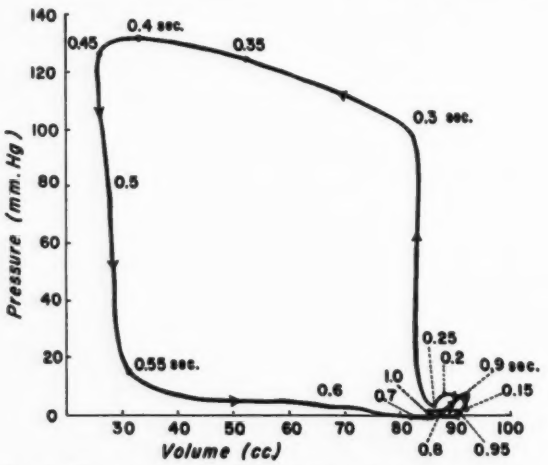


FIG. 7. Time course of left ventricular volume and pressure.

internal force upon the ventricular wall is one-fourth the total radial force acting upon the wall.

For example, consider a sphere such as a ventricle filled with blood under pressure. If the sphere were cut in half and the cut surface were closed with a diaphragm (fig. 5), the force exerted against the diaphragm would be

$$F = \text{area of diaphragm} \times \text{pressure}$$

or

$$F = \pi r^2 P$$

This force, which is one-fourth the lateral force exerted against the wall, is supported by

the wall at the edge (fig. 5, b and b′) of the cut sphere to which the diaphragm is attached, or, in the case of the ventricle, the muscle fibers. It is interesting that the muscle fibers need to exert a force of contraction which is only one-fourth as great as any given load which tends to force the ventricular wall outward. This is a peculiar advantage which the muscle fibers of the heart possess because of the shape and nature of the function of the heart as a pump.

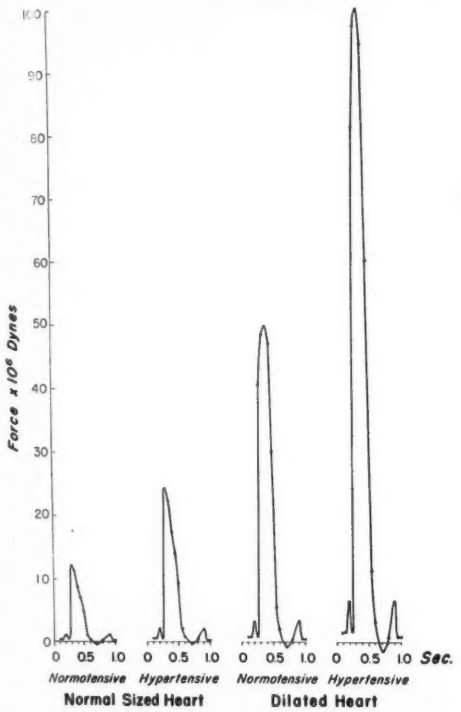


FIG. 8. The time course of total force acting against the wall of a normal sized and dilated heart with and without hypertension during a cardiac cycle. It is evident that dilatation and hypertension increase the "load" on the heart and that dilatation increases this load much more than the elevation in blood pressure.

RATES OF CHANGE IN INTRAVENTRICULAR PRESSURE AND IN VOLUME

The curves of the average normal time course of pressure and volume within the left ventricle[1] are shown in figure 6, as well as the time courses of the first and second derivatives with respect to time of pressure and volume. These curves are self-explanatory; the first derivative is a rate curve and the second an acceleration curve.

The relationship between the intraventricular pressure and volume for the average normal heart shown in figure 7 was obtained from the simultaneous pressure and volume curves of figure 6. This interesting curve shows that early in systole, during the phase of isometric contraction, there is a rapid rise in intraventricular pressure without any change in volume. During the ejection phase pressure changes slightly, whereas volume decreases rapidly. Then there is a rapid reduction in pressure with only a slight increase in volume,

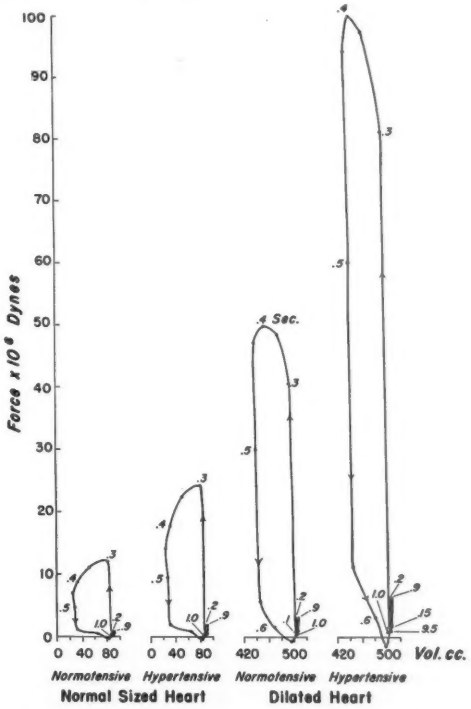


FIG. 9. The force-volume curves for a normal sized and dilated heart with and without hypertension during a cardiac cycle. The numbers along the force-volume "loops" indicate time in seconds during the cardiac cycle. The arrows indicate chronologic sequence.

and finally there is a rapid rise in volume with continued reduction in pressure as the ventricle fills during diastole. Incidentally, this latter hemodynamic state indicates a "suction" action of the ventricle.

Figures 8, 9 and 10 show the time courses of force, force-volume, and force-pressure for both the normal sized and dilated hearts with and without hypertension. The blood pressures employed for these calculations were 126/70 and 252/120 and the diastolic volumes were 85 cc. and 500 cc. respectively. The stroke volume was 60 cc. in each instance. It was

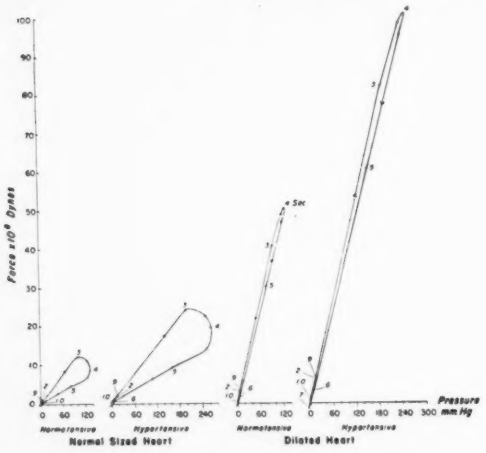


FIG. 10. The force-pressure curves for a normal sized and dilated heart with and without hypertension during a cardiac cycle. The numbers along the force-pressure "loops" indicate seconds during the cardiac cycle. The arrows indicate chronologic sequence.

assumed that the volume-pressure time course was the same as that of the normal heart shown in figure 7. These illustrations (figs. 8, 9 and 10) are self-explanatory.

WORK AND POWER

By integration of the pressure-volume curve of figure 7, the accumulated work or energy-time curve of figure 11*A* was obtained. It is evident from the curve that in this case a maximum value for work was reached at about the 0.25 second after the beginning of ventricular systole, after which there was a gradual and fairly constant decline in the work curve. There is "negative work" or an accumulation of potential energy by the ventricles during ventricular diastole and atrial systole. Figure 11*B*, the time course of the first derivative of the work curve with respect to time, shows the

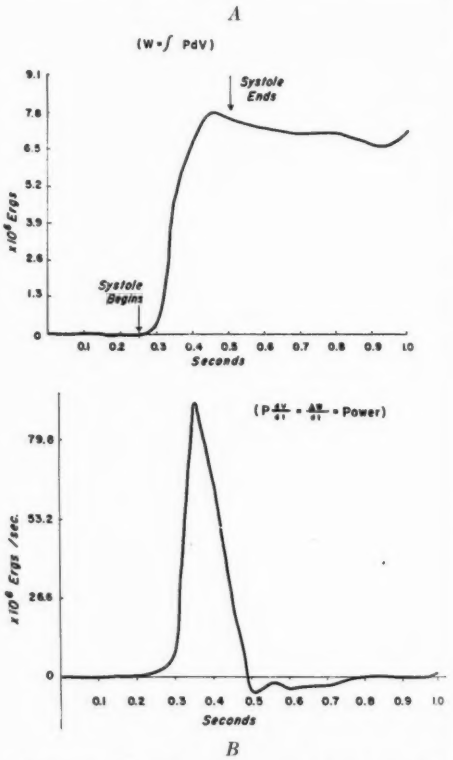


FIG. 11*A*. Time course of accumulated work of the left ventricle. This curve was obtained from the trace shown in figure 7. Figure 7 is a volume-pressure time course obtained from the volume and pressure curves of figure 6 (based upon figure 81, page 206, of Best and Taylor[1]). The slight decrease in accumulated work shown before the end of systole may be due to an artefact in recording of the ventricular volume curve during the protodiastolic phase.

B. Time course of power (first derivative of work curve).

rate of work performed (or power output) from moment to moment during the cardiac cycle. Primarily for curiosity, the first, second and third derivatives of the power curve were plotted as functions of time in figure 12*A*, *B*, *C*. Thus, power was maximal early in systole, declining later and reaching practically zero

during diastole. The greatest rate of change in power occurred during the period of reduced ejection of the cardiac cycle when it rapidly declines. The resemblances of the plots (fig. 12*B*, *C*) to the ballistocardiogram are self-

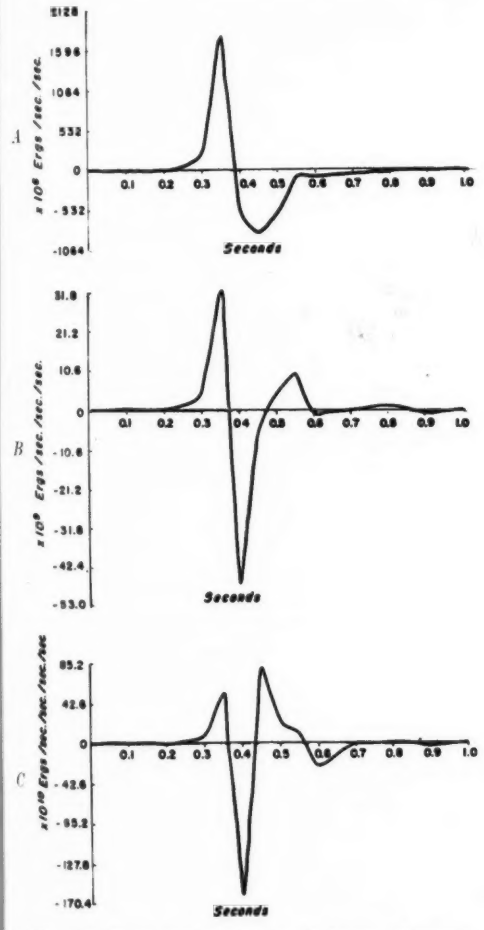


FIG. 12. Time course of rate of change of power. *A*. First derivative of power curve. *B*. Second derivative of power curve. *C*. Third derivative of power curve.

evident and will not be discussed. The significance of such curves remains unknown.

THE TRABECULAE CARNEAE AND PAPILLARY MUSCLES

The muscle fibers in the trabeculae carneae certainly contribute to the energy or force involved in pumping blood. The papillary muscles not only assist in emptying the ventricle by pulling the walls of the ventricle to which they are attached toward the center of the ventricular cavity but also aid in maintaining proper closure of the atrioventricular valvular leaflets. They must pull the apex and

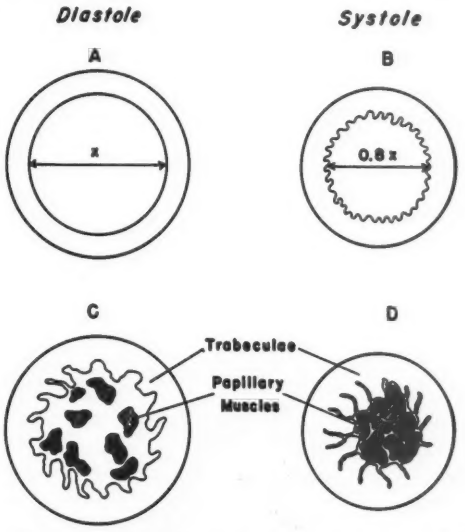


FIG. 13. Displacement of intraventricular luminal space by papillary muscles and trabeculae carneae.

A is a diagram of a cross section through a thick-walled sphere of diameter X. If this sphere were to contract due to shortening by 20 per cent of its fiber components, its diameter would reduce 20 per cent and its internal wall, at least, would tend to wrinkle, *B*. *C* is a diagrammatic cross section through a normal ventricle during diastole showing the papillary muscles, trabeculae carneae and the ridges and valleys of the irregular internal surface. During systole the luminal space and therefore contained blood is displaced by the mass of papillary muscle and trabeculae carneae and the internal irregular surface "folds" in a predetermined fashion. *D*. See text for details.

walls of the heart toward the atrioventricular valves or the valves toward the apex and walls of the heart.

These structures also assist in emptying the ventricle of blood more completely. For example, the muscle fibers encircle the cardiac lumen and since they can shorten only about 20 per cent[3, 4] of their resting length, they can reduce the diameter of the cardiac lumen

about 20 per cent during systole (fig. 13). This would not completely empty the heart. Under such circumstances the heart would be only partially emptied, about 50 per cent of its diastolic luminal volume remaining (fig. 13*A*, *B*). If the internal surface of the heart were smooth, shortening of the circumference of the outer and inner walls might cause the internal wall to wrinkle. If there were a smooth internal surface during diastole and this surface were squeezed upon and wrinkled during cardiac systole, it is possible that the subendocardial layer of myocardium would be injured with each cardiac contraction. However, the internal surface of the ventricles is extremely irregular and consists of ridges and valleys produced by the trabeculae carneae and the large papillary muscles. Consequently, when cardiac muscle shortens in length by 20 per cent, the normal heart is emptied much more completely of blood. The volume of blood that would have remained is displaced by the space occupied by the trabeculae carneae and papillary muscles (fig. 13*C*, *D*). These space-occupying muscular structures reduce considerably the residual space that is available for blood at the end of systole. Furthermore, because of the extremely irregular internal surface of the ventricles produced by the trabeculae carneae, wrinkling of the internal surface during systole is unnecessary and damage to the subendocardial layer of muscle is less likely. At the end of ventricular systole the ridges of muscular trabeculations are squeezed more closely together and the valleys are reduced in volume, thus displacing blood from these valleys and thereby reducing the volume of residual blood. Figure 14 shows cross sections of a normal heart and indicates the magnitude of the space displaced by the trabeculae carneae and papillary muscles. One can visualize the mechanics of these phenomena.

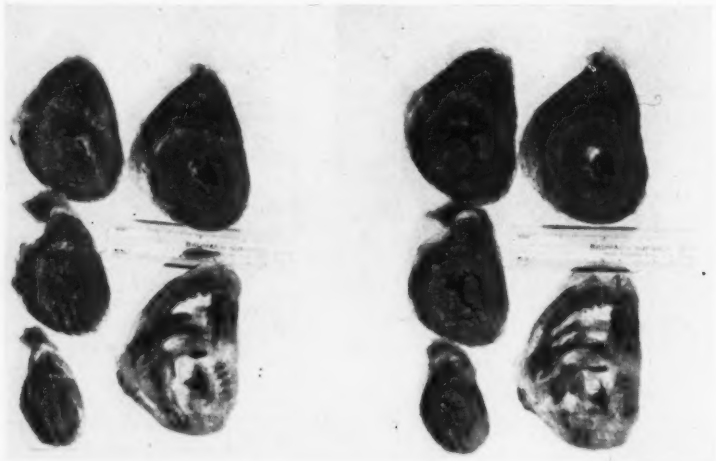


FIG. 14. Relationship of size of ventricular lumen to size of papillary muscles and trabeculae carneae. Photographs of cross sections through the ventricle of a normal heart in the contracted, *A*, and the more relaxed, *B*, state. These show how the papillary muscles and trabeculae carneae displace blood from the lumina of the ventricles by occupying space.

In the abnormally large and dilated heart the internal surface tends to become smooth. The relative volume of the lumen of the ventricle to that of the trabeculae carneae and the papillary muscles is so large that the relative space occupied by the trabeculae carneae and the papillary muscles is small. Therefore, in the dilated heart the size of the ventricular lumen remains large at the end of systole, so that amount of residual blood is also large and there is no need for trabeculae carneae and papillary muscles to displace blood to maintain the usual stroke output. Furthermore, the need or tendency for wrinkling to occur during

systole is less. In summary, therefore, the papillary muscles and trabeculae carneae displace blood from the adult heart in the same manner as cardiac jelly does from the embryonic heart.[4, 5]

It is also important to note that the borders of a large dilated heart, for the same stroke volume as a normal heart, should be expected to move relatively little. As stated previously, the volume of a sphere is equal to $4/3\pi r^3$. Therefore, if the volume of each systolic ejection is 60 cc. and the heart is large and dilated, the borders of the heart would move only slightly in association with this change in volume of 60 cc. This should be remembered when extreme cardiac enlargement is being differentiated from pericardial effusion. Both units of mass would reduce equally in volume per given stroke output.

Comment

It is necessary to remember that assumptions were made so that the concepts could be presented as simply as possible. The heart, of course, is not a perfect sphere and it probably contracts by a wringing type of motion. Its cavity is irregular. The time course of pressure and volume must vary with disease states and from time to time in the same subject and, therefore, only general ideas can be considered. The individual and specific circumstances certainly are different, tending only to approach the generalizations made in this presentation. These and similar considerations are certainly interesting and are probably important in cardiac function. It is also well to note that in the large dilated heart the percentage of shortening per muscle fiber required during systolic ejection of a given volume of blood is considerably less than that in a heart of normal size. One might find this comparable to the advantage offered by a system of ropes and pulleys employed in lifting a load or mass; the work is facilitated but the energy expended is greater. Studies have shown oxygen consumption to be greater for a given cardiac output in the large dilated heart than in the normal one.[6, 7]

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Obesity, Fat Metabolism and Cardiovascular Disease

By JOHN W. GOFMAN, M.D., Ph.D., AND HARDIN B. JONES, Ph.D.

Lipoproteins of the S_f 12–100 class, representing only about 10 to 15 per cent of the serum cholesterol, are strongly associated with atherosclerosis. The major independent contributions to this association are from the S_f 12–20 lipoproteins and the S_f 35–100 lipoproteins. The S_f 20–35 lipoproteins are primarily associated by virtue of their intercorrelation with the other classes. Obesity is moderately associated with the S_f 35–100 and definitely, but to a lesser degree, with the S_f 12–20. The association of obesity with total serum cholesterol is so low as to obscure the stronger association with the S_f 35–100 lipoproteins. The relationship of the S_f 12–100 lipoproteins with obesity may be adequate to explain the major share, if not all, of the association of obesity with atherosclerosis. The control of obesity should therefore be a prime consideration in the management of atherosclerosis and its complications.

THE CLINICAL association of obesity with the occurrence of cardiovascular disease has been extensively reported and is quite generally accepted. Yet the exact mechanism by which obesity facilitates the development of vascular disease has remained obscure, except for speculation on the possible physical burden of the excess adipose tissue. Atherosclerosis is the underlying basis for the major fraction of degenerative vascular disease. In several previous reports[1–6] concerning serum lipid transport via lipoproteins, we have established that certain special classes of lipoproteins are closely associated with the development of human atherosclerosis. It was of obvious interest to determine whether obesity is significantly related to the serum levels of atherosclerosis-associated lipoproteins, and whether any such relationship might explain the role of obesity in atherosclerogenesis. The data of this report show that such a relationship of obesity with certain classes of lipoproteins does exist and may adequately explain the excessive atherosclerosis associated with the obese state.

Recently we have reported[6] that two major classes of lipoproteins, the S_f 12–20 class and the S_f 20–100 class, provide essentially the entire contribution of serum lipids to atherosclerosis. In toto, the cholesterol of these two classes represents only approximately 10 to 15 per cent of the total serum cholesterol. The remaining 85 to 90 per cent of the serum cholesterol is not significantly associated with atherosclerosis.* Neutral fat is a prominent structural component of the S_f 20–100 class of lipoproteins, whereas it is low in the S_f 12–20 class. Cholesterol and cholesterol esters are more prominent constituents of the S_f 12–20 class than of the S_f 20–100 class. Of the two classes of lipoproteins, the S_f 12–20 class is more stable in level, being unaffected acutely by food intake. The S_f 20–100 class, especially the lipoproteins from S_f 35 to S_f 100, are more labile in level, showing appreciable increases with the ingestion of fat. However, in individuals with a moderate or severe degree of the lipid metabolic error previously described,[4, 5] the S_f 20–100 class of lipoproteins is more stable in concentration and is present at moderate or high levels even in the postabsorptive state. In spite of the individual

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*The S_f 8–10 and S_f 10–12 lipoproteins are associated with atherosclerosis. However, they are very closely related to the S_f 12–20 lipoproteins, so that generally no change in ranking occurs if they are not measured. If the S_f 8–12 lipoproteins are included, the remaining unassociated cholesterol is closer to 80 or 85 per cent.

variability in serum S_f 20–100 level, it has been possible to demonstrate unequivocally[6] the independent association of this class of lipoproteins with atherosclerosis to a degree essentially equivalent to that of the S_f 12–20 class of lipoproteins.

Earlier crude inspection of the data indicated that there was no marked relationship between estimated obesity and the serum S_f 12–20 lipoprotein level. In this study we have been able to make a precise evaluation of the relationship within the limits of the collected data for both the S_f 12–20 and S_f 20–100 lipoproteins with obesity. The group considered consists of 241 normal men 41 to 50 years of age in whom height, weight, serum S_f 12–20 and S_f 20–100 lipoproteins,* and total serum cholesterol were measured. As an estimation of obesity subjects were rated in pounds above and below the normal values from the height-weight data of Armstrong.[7] Lipoprotein analysis by the ultracentrifugal method[1] and serum cholesterol analysis were made on aliquots of the same serum sample. A summary of the quantitative relationships found is given in table 1.

It is evident from the data of table 1 that there is definitely a significant positive correlation between serum S_f 35–100 lipoprotein level and estimated obesity. This is the strongest relationship with estimated obesity observed in these data. The over-all S_f 12–100 lipoprotein level correlates positively with estimated obesity nearly as well. However, a significant, but much weaker, relationship is seen between serum S_f 12–20 level and estimated obesity.

There is a trend in the same direction in the relationship of total serum cholesterol with obesity, but quantitatively this relationship is of only borderline significance. It is to be noted that the measurement of total serum cholesterol alone would obscure the much stronger relationship of the S_f 35–100 lipoprotein level with estimated obesity. The data are expressed in a practical way below, assuming rectilinear regression between the various levels measured and estimated obesity.

Average increase per pound above ideal weight	Mg. per 100 cc.
S_f 35–100	0.7
S_f 12–20	0.2
S_f 12–100	1.2
Total Cholesterol	0.27

While these observations bear out the earlier impression of the very low correlation of

TABLE 1.—*The Quantitative Relationships of Serum Lipoproteins and Cholesterol with Obesity*

	No. of Cases	Sf 12–20	Sf 35–100	Sf 12–100	Total Cholesterol
Above Normal Wt.	199	47.6 ± 2.03*	68.3 ± 3.1	147.8 ± 6.0	264 ± 3.6
Below Normal Wt.	42	36.3 ± 2.9	43.1 ± 6.6	102.2 ± 9.6	245 ± 8.8
Probability that difference is not significant		<.01	<0.01	<0.01	~0.05
Standard deviation for entire group.	241	27.4	44.4	82.6	52.7
Intercorrelation with obesity (r)†	241	0.14 ± .065‡	0.28 ± 0.065	0.27 ± 0.065	0.095 ± 0.065
Probability that correlation is not significant		<0.02	<0.01	<0.01	~0.10

* Values are given as the mean plus or minus the standard error of the mean, which is calculated from the equation

$$\sigma_{SE} = \frac{\text{standard deviation of distribution}}{\sqrt{N-1}}$$

† r is the Pearson product-moment correlation coefficient.

‡ The standard error is that used in null-hypothesis testing for the significance of a correlation coefficient. Thus

$$\sigma_{SE} = \frac{1}{\sqrt{N-1}}$$

* Of the S_f 20–100 lipoproteins the S_f 35–100 provide the major independent contribution, although the S_f 20–35 lipoproteins are associated with atherosclerosis.

the S_f 12–20 level with estimated obesity, the slight relationship is a significant one and has bearing upon atherogenicity. The much higher relationship of the S_f 35–100 molecules with estimated obesity has real implications for atherosclerosis. Crudely, obesity accounts for approximately 8 per cent of the relationship of the S_f 35–100 lipoproteins with atherosclerosis, a relationship previously demonstrated to be a reasonably high one.[6] Since obesity was estimated here by height-weight relationships (at best a crude approximation to its assessment), and since there are biologic and technical variations in the estimate of the S_f 35–100 level, it is highly probable that the over-all S_f 35–100–obesity relationship is of the order of twice the measured one. This might then indicate that about 15 to 20 per cent (or more) of the relationship of the S_f 35–100 lipoproteins with atherosclerosis is accounted for by obesity. Further, since the relationship of S_f 35–100 level with obesity is only of moderate degree, we may infer that for some patients obesity is contributing far more than the estimated 15 to 20 per cent, whereas for others it contributes much less. The relationship of obesity with the other atherosclerosis-associated lipoproteins, the S_f 12–20 class, while of lesser degree than that for the S_f 35–100 class, is still appreciable and hence is of real importance for at least a segment of the population.

There are several possible explanations for the association of elevation of S_f 35–100 lipoproteins with obesity. In previous work[5] we have actually observed an acute rise in level of such molecules in the first several hours following a high fat meal. Thus the obese individual, who commonly ingests excessive quantities of dietary fat, may have part of his elevation through either the dietary fat excess itself or a slowed removal of dietary fats from the blood to tissues. Neither of these is exclusive of the possibility that there is at steady state a greater re-entry of fats from tissue depots into this part of the blood lipid transport mechanism as a feature of fat metabolism of the obese state itself as compared with the nonobese.

Significance of the S_f 35–100– and S_f 12–20–Obesity Relationship in Atherosclerotic Cardiovascular Disease

The clinical vascular consequences of atherosclerosis, such as coronary occlusion, are, in a general way, dependent upon the degree of atherosclerosis and atherosclerotic activity. Inasmuch as a large fraction of the "normal" population shows moderate to severe atherosclerosis,[8] we may anticipate that *small increases* in degree of atherosclerosis or atherosclerotic activity may be all-important in determining whether atherosclerosis will remain silent or will result in a frank clinical manifestation. The relationship of obesity to the S_f 35–100 lipoproteins especially (and its lesser relationship to the S_f 20–35 and S_f 12–20 lipoproteins) is of sufficient degree to account for a small, but definite, part of the association of these lipoproteins with atherosclerosis. Observations made in patients before and after reduction in weight have shown definite lowering of the S_f 35–100 lipoprotein levels in many subsequent to weight reduction. To what extent this is due to lowered dietary fat ingestion rather than to the reduction in weight itself in a specific case can not now be definitely answered.

The possibilities of lessening the clinical hazards incident to atherosclerosis through the control of obesity are of promise, and provide a sound rationale for the already clinically-established practise of advising weight reduction in the obese. While every patient will not respond, a certain proportion may be anticipated to show large responses in their lipoprotein levels, and hence, in all likelihood, in their atherosclerotic potentialities.

Summary

1. Of the two classes of serum lipoproteins which are strongly associated with atherosclerosis, the S_f 35–100 class is moderately related to obesity, whereas the S_f 12–20 class shows a much lesser, yet significant, relationship to obesity.

2. The positive correlation of atherosclerosis-associated S_f 35–100 and S_f 12–20 lipoproteins

with obesity provides part of the basis, and possibly the largest part, of the relationship of obesity with atheromatous vascular disease. This subtle relationship is almost entirely obscured by the total serum cholesterol measurement.

3. The control of obesity, as a prophylactic and therapeutic measure in atherosclerosis, already a part of clinical practice, derives support from the finding of the association of certain lipoprotein classes with obesity.

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Studies in Experimental Pericardial Tamponade

Effects on Intravascular Pressures and Cardiac Output

By JAMES METCALFE, M.D., JOHN W. WOODBURY, M.D., VICTOR RICHARDS, M.D., AND C. SIDNEY BURWELL, M.D.

As intrapericardial pressure is increased by the introduction of saline into the pericardial cavity, cardiac output falls. Intravascular pressures, arterial and venous, pulmonary as well as systemic, approach the same value. This equalization of intravascular pressure is due to the decreasing ability of the heart to maintain normal distribution of blood within the vessels.

AS EARLY as 1889 Cohnheim[1] demonstrated by injecting oil into the pericardial cavity that an increase in intrapericardial pressure causes a rise in peripheral venous pressure and a fall in peripheral arterial pressure. These same effects of cardiac tamponade have been confirmed by many others both in the experimental animal[2-11] and in patients with pericardial effusion.[12-15]

Cohnheim performed his experiments in curarized dogs with open chests, and under these conditions he observed a fall in pulmonary arterial as well as systemic arterial pressure. Moreover, he reasoned that pressure in the pulmonary *vein* must also fall, although he did not record the measurement of pulmonary venous pressure. He states "... and since in our experiment, as shown by the pulmonary curve, the right heart sends an abnormally small quantity of blood into the arteries of the lungs at each systole, the *arterial pressure must fall, and with it**—despite the impediment to the entrance of venous blood into the heart—*the tension in the pulmonary veins.*"* Simultaneous measurements of both pulmonary arterial and pulmonary venous pressures in experimental pericardial tamponade have not been recorded to our knowledge, although Nerlich[16] has reported a rise in left atrial pressure very similar in magnitude to a simultaneous rise in right atrial pressure. Therefore, a study of intravascular pressure changes in pericardial tamponade has been undertaken, and simultaneous measurements of pressures throughout the circulation, both systemic and pulmonary, will be presented.

METHOD

Dogs were anesthetized with intravenous Nembutal, and the thorax opened during positive pressure artificial respiration. A slit was made in the pericardium, and one plate of a split perforated plastic button† was slipped within the pericardial cavity. The second plate, machined to oppose the presenting surface of that within the pericardium, was screwed tightly to the latter by means of a special applicator. The screw was hollow and attached to the center of the intrapericardial plate. One end of a polyethylene tube was connected to the channel leading into the pericardium; the other end was led outside the thorax through a stab wound in the chest. In many of the dogs a small-diameter polyethylene tube was introduced into a pulmonary vein by way of one of its branches, the tip lying in a main pulmonary vein proximal to its entrance into the pericardium. The

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* Italicized in the original.

† The button used in these experiments was designed by Dr. Charles A. Hufnagel, Georgetown University Medical Center, Washington, D. C.

free end of this tube was led out of the chest by the same stab wound as that conducting the pericardial tube. The chest was then closed, the lungs having been fully inflated, and spontaneous respiration was allowed to resume. Cannulas were placed in a femoral artery and vein, and a cardiac catheter was introduced into a pulmonary artery. It was inserted by way of an external jugular vein, and passed through the right heart under fluoroscopic guidance. In many dogs a second catheter was passed to the right atrium. Saline manometers were used routinely to measure femoral venous and intrapericardial pressures, and in some instances to measure pulmonary venous pressure. Electromanometers were used to measure femoral arterial, pulmonary arterial, and right atrial pressures in all instances and in several experiments to measure "pulmonary capillary" and pulmonary venous pressures. The free end of the tube leading through the chest wall into the pericardial cavity was attached to a Y-connector, the other two arms of which were connected, respectively, to a saline manometer and a large reservoir of saline. Intrapericardial pressure was increased by raising the reservoir to the level desired. After several minutes of waiting to allow for inflow the reservoir tube was clamped and the intrapericardial pressure read from the saline manometer. While other measurements were being made the reservoir tube was left open so that, in spite of stretching of the pericardium or absorption of injected fluid, the intrapericardial pressure was maintained at the desired level. Postmortem examination was performed routinely and leakage from the pericardium was excluded in every case. All manometers, both saline and electrical, were set to the same zero point, the level of the dog board. Mean values were obtained by electrical integration for pressures recorded with electromanometers, and by averaging the extreme values for pressures obtained by saline manometers. Comparison of median pressures obtained arithmetically by the saline manometers with mean pressures obtained by electrical integration by the electromanometers does, of course, introduce an error. It is believed that our reported measurements are accurate to ±2 mm. Hg. No attempt has been made to quantitate this error, since the changes in pressure to be reported are beyond the error involved in their measurement.

In eight dogs, the cardiac output was determined by the direct Fick method at selected points of intrapericardial pressure. Expired air was collected for three or more minutes in a Douglas bag through a balloon-sealed intratracheal tube, and oxygen consumption calculated. Blood samples were taken simultaneously from the femoral artery and the pulmonary artery over a one-minute period beginning one minute after the start of collection of the expired air. Analysis of these samples permitted calculation of the arteriovenous oxygen difference.

Results

Peripheral Arterial Pressure. The effect of pericardial tamponade on the femoral arterial pressure was observed in 18 dogs. In figure 1, mean femoral arterial pressures of four dogs are plotted against intrapericardial pressure. The curves shown are representative of all. It is to be noted that femoral arterial pressure is maintained during moderate cardiac tamponade, but eventually falls precipitously, in some experiments to a level almost as low as or equal to intrapericardial pressure. There is also a progressive reduction in pulse pressure seen in every case as pericardial pressure is increased.

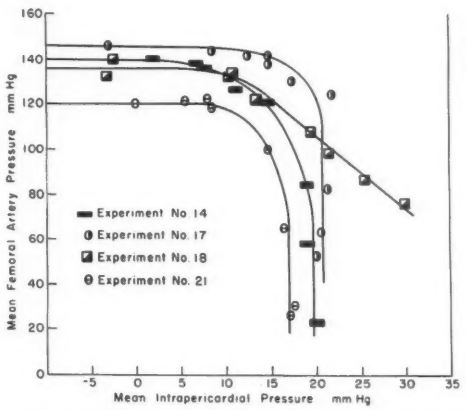


FIG. 1. Relation of femoral arterial pressure to intrapericardial pressure in pericardial tamponade.

Peripheral Venous Pressure. Mean femoral venous pressure was measured in 18 dogs, and the values obtained are plotted in figure 2. Pressure in the peripheral veins begins to rise as intrapericardial pressure approaches the resting venous pressure, and the venous stays above the intrapericardial, although by an ever decreasing increment, until both reach the same level at the height of tamponade. The pressure attained in the femoral vein as flow is brought to a standstill is in the region of 20 mm. Hg.

Right Atrial Pressure. The mean right atrial pressure as recorded in eight dogs is similarly plotted in figure 3. Right atrial pressure rises with increasing intrapericardial pressure in the same manner as peripheral venous pressure.

However, the right atrial mean pressures are slightly lower than simultaneous venous levels. The pressure gradient between femoral vein and right atrium gradually decreases throughout the experiment, until the two pressures become equal at maximum tamponade.

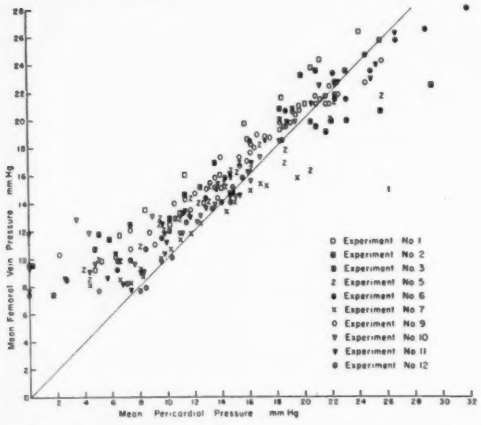


FIG. 2. Relation of peripheral venous pressure to intrapericardial pressure in pericardial tamponade. In figures 2, 3 and 4 the diagonal line is the line of equality of intravascular and intrapericardial pressures.

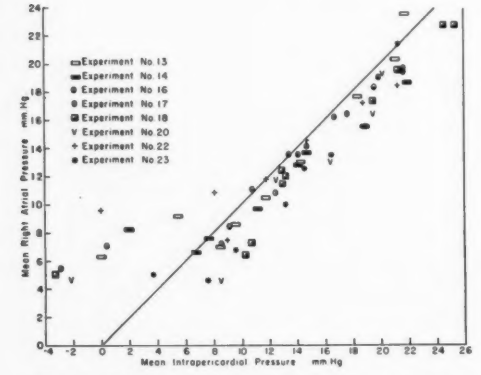


FIG. 3. Relation of right atrial pressure to intrapericardial pressure in pericardial tamponade. See legend to figure 2.

Pulmonary Venous Pressure. In figure 4, mean pulmonary venous pressure as measured in 12 dogs is plotted against intrapericardial pressure. These mean pressures, whether obtained by averaging the extreme values measured with a saline manometer or by electrical integration with an electromanometer, are observed to rise as intrapericardial pressure is increased. It may be noted that the pressures in the pulmonary veins and right atrium are generally of the same order of magnitude and that when there is a difference between them, the pulmonary venous pressure is slightly higher than the right atrial pressure. The pressure attained in the pulmonary veins at the height of tamponade is in the range of 20 mm. Hg. In several dogs "pulmonary capillary" pressure was measured according to the technic of Hellems and co-workers.[17] In each of these cases, "pulmonary capillary" pressure rose during tamponade in exactly the same manner as pulmonary venous pressure.

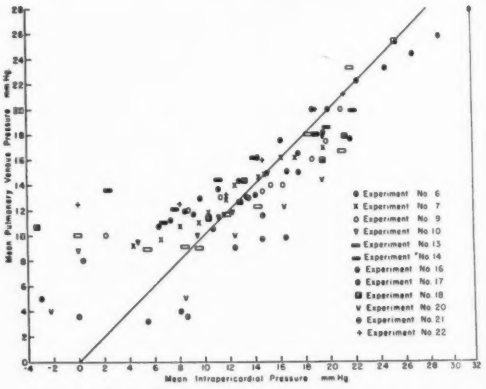


FIG. 4. Relation of pulmonary venous pressure to intrapericardial pressure in pericardial tamponade. See legend to figure 2.

Pulmonary Arterial Pressure. By analogy with the systemic circuit, one would expect the pulmonary arterial pressure and the pulmonary venous pressure to approach the same point as tamponade is produced. This does occur, as observed in eight dogs, but whether pulmonary arterial pressure rises or falls to approach this point depends upon the mean pressure level in the pulmonary artery before the induction of tamponade. In some dogs there is a decline, that is, the mean pulmonary arterial pressure is lowered by the procedure, but in most experiments the mean pulmonary arterial pressure eventually rises as the circulation is brought to a standstill. Since the "normal" mean pulmonary arterial pressure is in

the same range as the pressure observed throughout the vascular bed when circulation has ceased, the changes produced in pulmonary arterial pressure by tamponade are not dramatic.

A clearer understanding of the circulatory dynamics of pericardial tamponade is obtained by examining the simultaneous changes in all pressures in a single dog during a single episode of tamponade. Figure 5 illustrates the effects of gradually increasing intrapericardial pressure on femoral arterial, pulmonary arterial, right

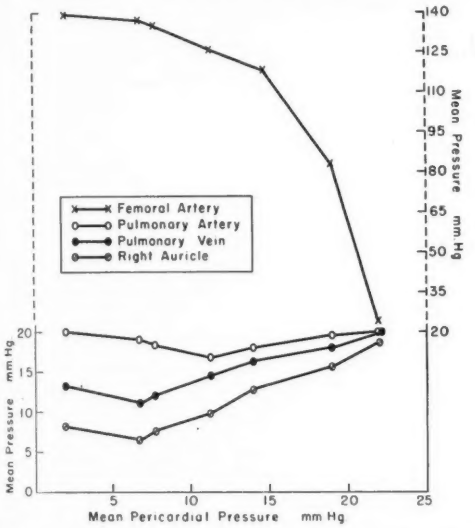


FIG. 5. Intravascular pressures in pericardial tamponade. Femoral arterial pressure is plotted on one scale noted on the right side of the figure, all other pressures on the scale noted on the left side.

atrial, and pulmonary venous pressures in a single dog. Right atrial and pulmonary venous pressures rise steadily as pericardial pressure increases. In this experiment pulmonary arterial pressure does not change significantly. In this animal, as in all, femoral arterial pressure declines, slowly at first, then more and more rapidly. All curves approach a single point at an intrapericardial pressure of 22 mm. Hg when all intravascular pressures are equal at about 20 mm. Hg. At this point the absence of any pressure gradients must mean that circulation has ceased. Even so, at this point the process is still reversible. If intrapericardial pressure is rapidly reduced, all intravascular pressures gradually return to their original levels, and for a time peripheral arterial pressure may actually exceed its pretamponade level.

The effects of changes in intrapericardial pressure may also be described by charting the intravascular pressure existing simultaneously at each of several points within the circulation. Figure 6 is a diagram of the mean intravascular pressures at five such points before

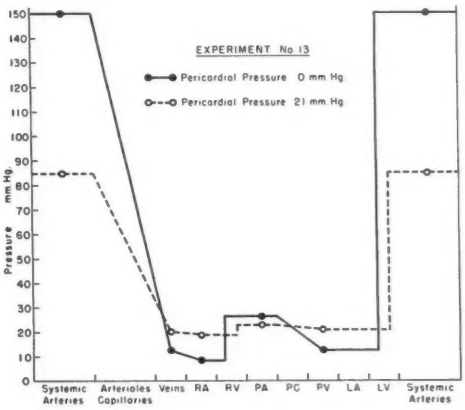


FIG. 6. Intravascular pressures in pericardial tamponade. Abbreviations used along the abscissa of this figure denote the following: RA, right atrium; RV, right ventricle; PA, pulmonary artery; PC, "pulmonary capillary"; PV, pulmonary vein; LA, left atrium; LV, left ventricle.

The spacing of the segments of the vascular bed is arbitrarily chosen for diagrammatic purposes. Straight lines are drawn between measured points. Because of the arbitrary abscissa, it is to be recognized that the resulting gradients are not quantitatively accurate.

and during pericardial tamponade. This diagram shows that as intrapericardial pressure is increased, arterial pressures fall and venous pressures rise. These changes in pressure are due to a decreasing effect of cardiac output upon the distribution of blood within the vessels. It is, therefore, necessary to consider the effects of changes in intrapericardial pressure upon the cardiac output.

Cardiac Output. As intrapericardial pressure is increased, cardiac output decreases (table 1). This fall in cardiac output is due to a pro-

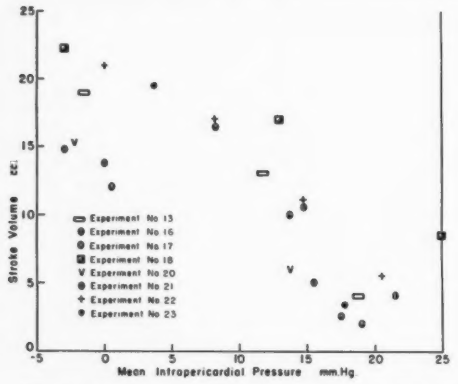


FIG. 7. Relation of stroke volume to intrapericardial pressure in pericardial tamponade.

TABLE 1

Dog Number	Pericardial Pressure mm. Hg	Cardiac Output L/min.	Pulse Rate beats/min.	Mean Femoral Arterial Pressure mm. Hg	Mean Right Atrial Pressure mm. Hg	Total Peripheral Resistance*
13	−2	3.3	175	143	7	41
	12	2.3	176	144	11	58
	19	0.7	180	88	16	103
16	0	2.2	183	142	7	61
	14	2.0	201	136	14	61
	19	0.3	167	102	18	279
17	−3	2.5	170	143	6	55
	15	2.0	190	140	14	63
	22	0.8	198	103	20	104
18	−3	3.0	137	135	7	42
	13	2.6	152	127	12	45
	25	1.5	177	95	24	46
22	0	3.6	168	150	9	39
	8	2.8	169	154	9	52
	15	2.1	188	137	14	59
	21	1.0	188	85	19	66

* The values given are those obtained by using the following formula:

$$Resistance = \frac{(Mean\ Femoral\ Arterial\ Pressure - Mean\ Right\ Atrial\ Pressure)}{Cardiac\ Output}$$

with pressures and cardiac output expressed in the units used in the table.

gressive decrease in stroke volume (fig. 7). The heart rate increases as tamponade is produced, but this increase is insufficient to maintain normal minute output. Figure 7 shows that stroke output approaches zero at an intrapericardial pressure of about 20 mm. Hg. This level agrees with the value at which all intravascular pressures become identical, as described earlier.

Peripheral Resistance. Comparison of the effect of increasing pericardial pressure on arterial blood pressure and cardiac output shows (table 1) that the arterial pressure is maintained early in the experiment when cardiac output has already declined. Maintenance of arterial pressure in the face of a decreased cardiac output can only be accomplished by an increase in peripheral resistance. That this occurs in pericardial tamponade has been shown previously[11, 15] and is demonstrated by the calculated values for peripheral resistance given in table 1.

The measurements of simultaneous pulmonary arterial and pulmonary venous pressures in these experiments permit calculation of the pulmonary resistance. Calculated pulmonary resistance during pericardial tamponade showed no change which was not explainable by the systematic error involved in measurement of the pressures and flow by the methods used.

DISCUSSION

The pressure within any segment of the vascular tree is determined by the capacity of that segment and the volume of the blood within it, whether that volume is put there momentarily by the action of the heart or lies stagnant when there is no effective ventricular propulsion of blood. As Starling pointed out, in pericardial tamponade intravascular pressures approach an identical (and therefore "flowless") point. This trend is explained by the steadily lessening ability of the heart to perform its function as a pump. As cardiac output declines, and finally ceases, the volume of blood within the vascular tree is redistributed until all pressures, systemic and pulmonary, arterial and venous, are identical. If at this point pericardial pressure is reduced, restoration of normal pressures is accomplished by restora-

tion of normal volume distribution by a recovery of cardiac function.

The mechanism by which pericardial effusion decreases cardiac output is not yet clear. Nerlich[16] has stressed the lessened gradient for venous inflow into the atria. Changes in resistance to flow within the heart have been inferred.[18] Such problems are at present under study in this laboratory.

Summary

1. Peripheral arterial, peripheral venous, right atrial, pulmonary arterial, and pulmonary venous (and occasionally "pulmonary capillary") pressures have been measured in dogs during experimental pericardial tamponade. Cardiac output was measured at selected points in many experiments.

2. With increasing intrapericardial pressure pulmonary venous pressure (and "pulmonary capillary" pressure) has been found to rise in every case. This rise in pulmonary venous pressure is of the same order of magnitude as the rise in right atrial pressure.

Depending on its resting value, mean pulmonary arterial pressure may remain unchanged, rise, or fall to approximate that level of pressure which exists throughout the vascular tree at the height of tamponade.

As intrapericardial pressure increases, all intravascular pressures, pulmonary and systemic, venous and arterial, approach the same value of about 20 mm. Hg.

3. Cardiac output falls as intrapericardial pressure is elevated. This is due to a decrease in stroke volume.

4. The equalization of intravascular pressure is due to a progressive decline in the performance of the heart in maintaining normal distribution of blood within the vascular tree.

Acknowledgment

Appreciation is expressed to Miss Barbara Jacobs and Miss Mary Jane Schumacher for expert technical assistance.

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Use of a Combination of Anion and Cation Exchange Resins in the Treatment of Edema and Ascites

By B. L. MARTZ, M.D., K. G. KOHLSTAEDT, M.D., AND O. M. HELMER, PH.D.

A mixture of a carboxylic acid type of cation exchange resin and a weakly basic anion exchange resin has been used successfully to control the edema of 42 patients with congestive heart failure and the ascites of 14 patients with cirrhosis of the liver. Approximately one-third of the cation exchanger was supplied in the potassium cycle.

Inclusion of the anion exchange resin resulted in a greater sodium uptake per gram of resin and apparently decreased the incidence of disturbances in acid-base balance in patients with impaired renal function who were treated with resins.

APPROXIMATELY 100 years ago two English agricultural chemists, Thompson[1] and Way,[2] recognized and studied extensively the principle of ion exchange as it applied to soil. They observed that when a water-soluble fertilizer such as ammonium sulfate or carbonate was added to soil, ammonia was retained and an equivalent amount of calcium released by some constituent of the soil. They concluded that aluminum silicates were responsible for this phenomenon. These reports stimulated the interest of other agricultural chemists, but not until the beginning of the twentieth century did the potential importance of ion exchange in industry become apparent. A German chemist, Gans,[3] is credited with providing the impetus for industrial application of ion exchange substances. Subsequent to his report, natural and synthetic silicates found wide use in purification and separation processes.

The versatility of application of the ion exchange principle was greatly increased by the discovery by Adams and Holmes[4] in 1935 that various synthetic resins, chemically similar to Bakelite, possessed ion exchange properties. These investigators demonstrated that certain resins exhibited an affinity for cations, others for anions.

From the Lilly Laboratory for Clinical Research, General Hospital, Indianapolis, Ind.

Read in part before the Twenty-fourth Annual Scientific Sessions of the American Heart Association, June 9, 1951, Atlantic City, N. J.

Synthetic resins are polymers of high molecular weight, sufficiently cross-linked to have a negligible solubility. The resin contains many accessible ion exchange groups, amine in the case of anion exchange resins, sulfonic or carboxylic in the case of cation exchangers.

The first application of ion exchange resins in clinical medicine was the employment by Segal[5] in 1945 of a polyamine resin (anion exchanger) to reduce gastric acidity in the treatment of peptic ulcer.

In 1946, William Dock[6] reported animal experiments showing that a synthetic cation exchange resin could be used to take up sodium from the intestinal tract, thus increasing fecal excretion of this element. He reported that 20 to 30 mg. of sodium per gram of resin was taken up when rats were fed 10 to 25 per cent of their diet as resin.

In 1949, Irwin, Berger, Rosenberg, and Jackenthal[7] reported on the effect of the administration of a sulfonic acid type of cation exchanger to human subjects. Marked increases in fecal sodium and potassium with concomitant decreases in urinary excretion of these ions were observed. An increase in ammonia and titratable acid excretion in the urine occurred during resin administration. Carbon dioxide concentration of the serum decreased and chloride concentration increased in their patients. Potassium deficiency was also encountered.

Kahn and Emerson[8] used both the sulfonic and the carboxylic acid type of cation exchange

resin in the treatment of edema. In one patient receiving as much as 100 Gm. of sulfonic acid resin per day, an abrupt fall in serum potassium and calcium occurred after approximately 50 days of therapy. One patient who did not exhibit the usually observed rise in ammonia excretion during resin therapy developed subclinical acidosis. These investigators found that equal parts of potassium and ammonium resin prevented excessive potassium depletion without interfering with sodium removal.

The subject of cation-exchange resins in the management of edema was recently reviewed by Dock and Frank.[9]

The carboxylic acid type of cation exchange resin was chosen for the studies herewith reported, because in vitro this resin has a greater *total* capacity and exhibits a greater cation uptake at pH levels encountered in the intestinal tract than the now available sulfonic acid resins.[10] Resin in the hydrogen rather than the ammonium cycle was used because of its greater palatability.

Methods

Patients with a severe grade of chronic congestive heart failure or with cirrhosis of the liver with ascites were selected as subjects for the clinical trial of ion exchange resins. They were hospitalized on a ward organized for metabolic investigation, and sodium and potassium balance studies were conducted. A graduate nutritionist directed preparation and serving of the food. Three day menus were prepared for 0.5, 1.0, and 1.5 Gm. sodium diets. The appropriate menu was then followed during each balance study conducted. Results of the analysis of food from a sample tray were found to vary as much as 15 per cent from the value obtained from food charts, but repeated analyses of the same menu varied within very narrow limits.

Feces were collected for three-day periods at the beginning and end of which carmine dye was administered. Only male patients were used in order to lessen the chance of contamination of feces with urine. Feces were collected directly into 4-liter beakers; single specimens were later combined for analysis of the three-day total. Daily 24-hour urine specimens were collected and analyzed for electrolyte content. Urine was preserved by addition of toluene and by refrigeration. Plasma electrolyte determinations were made, as indicated, at one- to seven-day intervals; a modified Beckman flame photometer was used for sodium and potassium analyses.

The analytic methods employed were as follows: digestion of food and feces, Peters and Van Slyke[11]; sodium and potassium in urine, Mosher and coworkers[12]; chloride in plasma, Schales and Schales[13]; chloride in urine, Harvey[14]; phosphate in urine and feces, Fiske and Subbarow[15]; sulfate in urine and feces, Fiske[16]; carbon dioxide content of serum, Van Slyke, Stadie and Neill[17]; ammonia in urine, Van Slyke and Cullen[18]; titratable acid in urine, Henderson and Palmer[19]; calcium in feces, Hawk, Oser, and Summerson.[20]

Following periods of observation in the hospital during which the effect of resin on renal and fecal excretion of sodium was investigated, patients received mixtures of resin as outpatients, and determination of sodium, potassium, chloride, and carbon dioxide in blood were made at weekly intervals.

Results

Cation Exchange Resins

Two normal subjects were given the carboxylic acid type of resin in the hydrogen cycle. In one individual receiving 15 Gm. of resin in 200 cc. of water three times daily, the amount of sodium in the feces during three days increased from 16 to 82 mEq. and the potassium content during the same period increased from 18 to 54 mEq. In this subject no change in plasma electrolytes was observed, but, in a second person given 15 Gm. of carboxylic resin four times daily for eight days, serum potassium declined from 4.5 to 2.9 mEq. per liter. Excretion of sodium for three days increased from 8 to 180 mEq. and the potassium excretion increased from 36 to 292 mEq. In both individuals a marked decrease in urinary excretion of sodium and potassium occurred during resin administration.

It was found that the decrease in serum potassium could be avoided by administering tablets of potassium chloride or by providing potassium in the form of the potassium salt of the resin. The latter proved to be preferable as the necessary amount of this cation could thus be supplied without increasing the anion intake.

The potassium salt of the carboxylic acid type of resin was administered to four patients in doses of 30 Gm. per day. This form of the resin was effective in removing sodium from the intestinal tract, as evidenced by a decrease in urinary sodium and an increase in urinary potassium equal to the potassium content of the resin administered. However, sufficiently large

TABLE 1.—*Changes in Fecal Excretion of Sodium during Administration of Ion Exchange Resins*

Patient No. Diagnosis	Dietary Sodium mEq./day	Resin Dosage Gm./day H	K	Anion	Fecal Excretion of Sodium mEq./day Total	Per Gm. Resin
Patient 1	83	control			3.9	
Rheumatic Heart Disease	113	40	20	0	42.7	0.65
Congestive Heart Failure	113	40	20	8	77.2	1.07
	113	50	25	0	24.0	0.27*
	113	40	20	8	97.1	1.37
	113	45	23	0	79.0	1.10
	113	control			4.6	
Patient 2	64	control			1.4	
Arteriosclerotic Heart Disease	114	30	15	6	78.1	1.50†
Congestive Heart Failure	113	30	15	6	75.6	1.45‡
	131	40	20	0	45.8	0.74*
	128	40	20	0	138.0	2.27
	121	40	20	8	150.0	2.18
Patient 3	66	60	15	0	43.6	0.55
Cirrhosis	84	60	30	0	58.8	0.63
	14	70	20	0	51.6	0.55
	65	70	20	0	58.8	0.63
	65	control			2.0	
	130	30	15	6	61.4	1.16§
	130	30	15	6	52.7	0.99¶
	127	34	17	0	60.7	1.15
	127	34	15	6	79.6	1.52
	127	control			1.3	
Patient 4	120	control			2.6	
Cirrhosis	39	65	10	0	26.8	0.32
	46	50	25	0	19.7	0.23
	41	50	25	8	57.9	0.66
Patient 5	65	control			3.1	
Arteriosclerotic Heart Disease	61	40	20	8	47.1	0.65
Congestive Heart Failure	62	40	20	8	55.9	0.77
	65	34	17	0	28.0	0.49
	65	30	15	6	57.0	1.05
	66	control			4.8	
Patient 6	133	control			0.6	
Severe Essential Hypertension	130	30	15	0	50.2	1.10
	134	40	20	0	57.1	0.94
	21	40	20	0	14.8	0.24
Patient 7	58	control			1.5	
Cirrhosis	58	40	20	0	32.0	0.51
	58	40	20	3	48.4	0.74
	113	40	20	8	81.4	1.17
Patient 8	133	control			7.0	
Essential Hypertension	133	40	20	0	58.8	0.86
Congestive Heart Failure						
Patient 9	113	40	20	8	83.7	1.18
Arteriosclerotic Heart Disease						
Congestive Heart Failure						
Patient 10	58	40	20	8	60.8	0.85
Essential Hypertention						
Patient 11	18	control			2.1	
Essential Hypertension	20	40	20	0	30.0	0.46
Congestive Heart Failure	43	40	20	8	43.8	0.61
Patient 12	152	control			2.5	
Normal	130	60	0	0	60.0	0.95

* Ammonium resin in place of hydrogen. † Resin administered with meals.
‡ Resin administered between meals. § Resin suspended in water. ¶ Resin suspended in milk.

doses to be useful therapeutically could not be given without exceeding the ability of the kidneys to excrete potassium. After approximately two weeks therapy in two of the above patients serum potassium concentration rose to 6 mEq. per liter.

Trial of various proportions of hydrogen and potassium resin revealed that with the mixture of one-third potassium resin and two-thirds hydrogen resin a sufficient amount of potassium was provided to maintain urinary excretion of this ion at approximately the same level as it had been prior to administration of resin. Concentration of potassium in the plasma remained normal.

This mixture of resin was used to control edema in 12 patients with severe congestive heart failure over a period of 2 to 13 months. The sodium excreted in the feces during resin administration varied from patient to patient and varied considerably with the degree of sodium restriction. (See table 1.) In patient 4, on a daily dietary intake of 1 Gm. of sodium, only 0.23 mEq. of sodium was taken up by each gram of resin. In patient 1, receiving approximately 3 Gm. of sodium per day, the resin removed 1.1 mEq. of sodium per gram. Analysis of six three-day stool specimens on four patients receiving a 3 Gm. sodium diet (patients 1, 2, 3, and 6 in table 2) showed an average sodium uptake of 0.96 mEq. per gram of resin.

During administration of resin, sodium excretion in the urine decreased markedly in all patients except those with cirrhosis of the liver in whom renal excretion of sodium had been low prior to resin ingestion. Urinary excretion of chloride remained relatively constant. A marked increase in urinary ammonia and titratable acid occurred on starting resin therapy and was maintained during its administration. In the majority of patients this resin mixture caused only a slight change in the carbon dioxide content of the serum and concentration of chloride in the plasma. However, in three patients with severe impairment of renal function, a marked increase in chloride and a decrease in carbon dioxide content occurred. Figure 1 illustrates the data obtained on such a patient. In this individual, who had congestive heart failure due to arteriosclerotic heart disease and rather markedly impaired renal function (urea clearance 28 per cent of average normal), a progessive lowering of the carbon dioxide content of the serum was observed. When it had decreased to 13.5 mEq., the resin was discontinued and this resulted in a prompt return of the carbon dioxide content to normal. Similar results were noted in two other patients. Substitution of the ammonium salt of the carboxylic acid resin for the hydrogen resin in the amount necessary for equal sodium removal did not decrease the acidotic tendency.

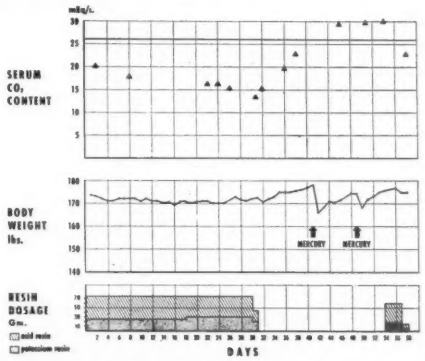


FIG. 1. *Acidosis Produced by Cation Exchange Resin.* In patient W. S. a lowering of carbon dioxide content occurred during treatment with cation exchange resin which had been started approximately one month prior to the beginning of this graph. When carbon dioxide content had declined to 13.5 mEq., resin was discontinued. Carbon dioxide promptly returned to a slightly elevated level. A second attempt at resin administration also resulted in a decrease in carbon dioxide content. When resin was discontinued a gain in weight promptly occurred necessitating the use of mercurial diuretics.

Use of Anion Resin with the Cation Exchanger

In an attempt to prevent lowering of the serum carbon dioxide content by increasing the fecal excretion of anions, it was decided to observe the effect of the administration of a mixture of the cation exchanger and a weakly basic anion exchange resin. When a mixture containing 12 per cent anion resin, 29 per cent potassium resin and 59 per cent hydrogen resin (Carbo-Resin)* was given to a patient who had developed acidosis on the cation exchange resin alone, the previously noted decline in carbon

* Sodium Removing Resins, Lilly.

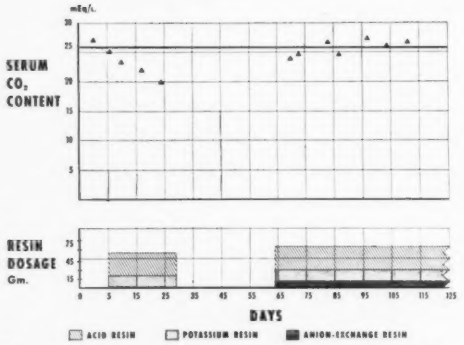


FIG. 2. *Prevention of Disturbance of Acid-Base Balance by Addition of Anion Exchange Resin.* L. M., a patient with congestive heart failure, exhibited a progressive decline in serum carbon dioxide content while receiving cation exchange resin. At a later date, although no measurable change in renal function had occurred, this patient received the same dosage of cation exchange resin mixed with 8 Gm. per day of anion exchange resin. Carbon dioxide content did not decrease.

TABLE 2.—*Fecal Excretion of Anions*

(mEq. per three days)

Patient: C. W. No. 256894 Dietary Sodium: 3 Gm. per day

	Without Resin	Resin: 60 Gm. per day	
		Cation Resin	Cation-Anion Mixture
Chloride	8	4	13
Sulfate	4	4	27
Phosphate	269	101	156
Total	281	109	196

Patient: W. S. No. 45875 Dietary Sodium: 1.5 Gm. per day

	Without Resin	Resin: 51 Gm. per day	
		Cation Resin	Cation-Anion Mixture
Chloride	10	6	15
Sulfate	3	17	23
Phosphate	200	98	154
Total	213	121	192

dioxide content did not recur, although no measurable improvement in renal function had taken place (fig. 2).

Effect on Fecal Excretion of Anions. Table 2 shows the effect of resin administration on the fecal excretion of chloride, sulfate, and phosphate. The menu for each patient was duplicated during the three periods of study. Dosage was the same during the two resin periods. The order in which the two types of resin were administered was varied to eliminate such factors as duration of therapy. During the period in which cation exchange resin was being taken, the concentration of anions in the feces declined. The addition of 12 per cent anion exchanger increased anion excretion (primarily phosphate) approximately 25 mEq. per day.

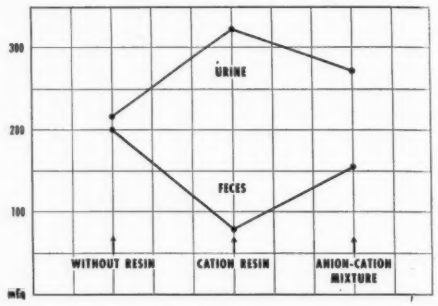


FIG. 3. *Effect of Resin Mixtures on Urinary and Fecal Excretion of Phosphates.* During daily administration of 51 Gm. of cation resin of the carboxylic acid type, urinary output of phosphates was approximately 100 mEq. greater than during the control period. At the same time, phosphates in the feces had decreased by approximately the same amount. The patient was then given the same dosage of cation-anion mixture and fecal excretion of phosphates increased and the amount eliminated in the urine decreased. Exactly the same menu was followed during each three-day period.

Thus, fecal excretion of anions approached but did not equal the control value. During the same study an inverse change in urinary excretion of phosphate was observed. This is illustrated in figure 3.

Effect on Sodium Uptake. The addition of the anion exchange resin also improved the uptake of sodium by the cation exchanger. In the six patients included in table 3 the fecal excretion of sodium was determined for a three-day period prior to the administration of resin, when cation exchange resin alone was given, and when a mixture of anion and cation resin was given. Each patient's menu was ex-

actly the same during all periods of study. In every instance the cation-anion mixture caused a greater fecal excretion of sodium even though the actual amount of cation exchange resin administered was less. Fecal excretion of potassium was also greater. The increased efficiency of the mixture was of the greatest amplitude in patients receiving the lower sodium diets. The increase in the sodium removing capacity obtained by adding anion resin to the cation exchanger is also illustrated in figure 4. This patient was in approximate sodium balance on a diet containing 1.5 Gm. of sodium, but when mEq. more than had been taken up by the cation exchanger alone. Thus, at this level of sodium intake, a 60 Gm. per day dosage of the cation-anion mixture would remove approximately 0.5 Gm. more sodium than an equal dose of the cation resin.

Effect on Calcium and Iron Metabolism. Frequent determinations of serum calcium, phosphorus, and alkaline phosphatase in patients receiving resin have revealed no significant deviation from normal. Comparative x-ray films before and after six to nine months of resin therapy in several patients have shown no detect-

TABLE 3.—*Effect of Dietary Sodium on Efficiency of Cation Resin and Cation-Anion Mixture of Resins*

Patient	Dietary Sodium mEq./day	Resin Dosage Gm./day	Fecal Excretion of Sodium (mEq.)				
			Control (No resin)	Cation Resin		Cation-Anion Mixture	
			per day	per day	per Gm. resin	per day	per Gm. resin
M. W.	41	75	2.6	19.8	0.23	58	0.74
W. S.	61	68	3.2	28.0	0.36	57	0.79
J. F.	58	60	1.5	32.0	0.51	81	1.3
C. W.	113	68	3.9	42.7	0.57	77	1.1
E. H.	127	51	2.0	60.0	1.1	79	1.5
F. J.	128	60	1.5	138.0	2.2	150	2.4

Uptake of sodium by resin is considerably greater on the more liberal sodium diets than on diets very low in sodium. In each of the patients listed the sodium removed per gram of resin was greater during administration of the cation-anion mixture than when the cation resin alone was given.

the salt intake was doubled, edema recurred. The administration of 60 Gm. of the cation exchange resin resulted in a marked increase in sodium content of the feces as shown in the second portion of the graph. When 8 Gm. of anion exchange resin was added, fecal excretion of sodium increased from 138 to 150 mEq. per day. The marked reduction in urinary excretion of sodium is also illustrated. When the same patient was given a mixture of the ammonium salt of the carboxylic acid resin and potassium resin for a period of two weeks and the balance study repeated, fecal excretion of sodium was only 45.6 mEq. per day. Fecal potassium was also less.

In five patients receiving a 3 Gm. sodium diet and the anion-cation resin mixture (patients 1, 2, 3, 7, and 9, table 1), analysis of 10 feces specimens, each collected over a three-day period, revealed an average sodium uptake of 1.26 mEq. per gram of resin. This was 0.3

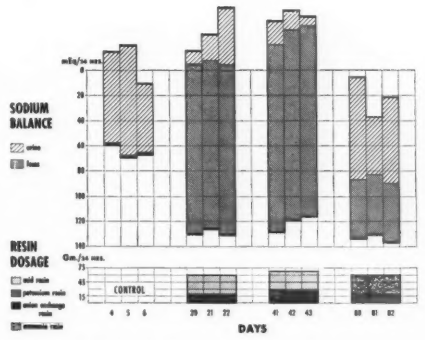


FIG. 4. *Effect of Various Resin Combinations on Sodium Balance.* Sodium balance studies during four three-day periods: without resin; with hydrogen and potassium cation exchange resin; with cation-anion exchange mixture, and with ammonium-potassium cation resins. Sodium intake is charted from the zero line downward. Fecal and urinary excretion of sodium are charted upward using the intake as the base line. Negative sodium balance is indicated by the portions of the graph extending above the zero line.

able change in the density of the small bones. Studies of the comparative fecal excretion of calcium in seven patients showed an average increase of 9.8 mEq. per day during resin administration.

Determinations of hemoglobin, red cell count and hematocrit on all patients receiving resin for prolonged periods have shown no evidence of anemia. One patient who had an iron deficiency anemia due to bleeding hemorrhoids at the time resin was started and who received simultaneously 0.3 Gm. of ferrous sulfate and 15 Gm. of Carbo-Resin four times daily manifested a normal hematopoietic response. The hemoglobin increased from 48 to 77 per cent; red blood cell count from 3,000,000 to 3,900,000 in one month.

Administration of Mercurial Diuretic during Resin Administration

Resin potentiates the effect of mercurial diuretics in patients with both congestive heart failure and cirrhosis of the liver. As an example, E. H., with severe cirrhosis, excreted 1800 ml. of urine containing 170 mEq. of sodium and 198 mEq. of chloride in the 24 hours after injection of 2 cc. of an organic mercurial compound. Later, at a time when the amount of edema and ascites was approximately the same and the sodium and water intake identical, but when the patient had been receiving a mixture of resins for six days, 3800 ml. of urine containing 330 mEq. of sodium and 400 mEq. of chloride was excreted in the 24 hours after the intramuscular injection of the same dose of mercurial diuretic.

Clinical Application

The mixture of anion-cation resin has been given continuously to 42 patients with congestive heart failure and to 14 patients with ascites due to cirrhosis of the liver for periods of not less than four months. In all but six patients the desired therapeutic effect was obtained. Four of these individuals could not tolerate sufficient quantities of the resin because of gastrointestinal disturbances related to their disease. In two others an exacerbation of pre-existing angina pectoris occurred during administration of resin.

A diet containing 1.5 Gm. of sodium (approximately 3.7 Gm. of sodium chloride) is suitable for starting treatment with resin. This amount of sodium permits the inclusion of most foods of the average American diet in quantities sufficient for adequate caloric intake. Certain foods and seasonings high in sodium must be avoided, and salt cannot be added to the food. The starting dosage of Carbo-Resin is 30 to 60 Gm. per day given in three to six equal parts.

In the average patient this regimen can be expected to produce a negative sodium balance. In the edematous patient, if daily loss of sodium is greater than intake, a decrease in body weight will occur. When the optimum weight is reached, either intake of sodium must be increased or resin dosage reduced. It is possible to deplete the body of sodium by excessive doses of resin or too rigid dietary restriction, producing the so-called "low salt syndrome." When resin is used in conjunction with a very low sodium intake, a greater portion of the cation exchange capacity is utilized in increasing fecal excretion of potassium, and depletion of this ion may be produced.

In patients with a severe grade of sodium retention it is often advisable to give mercury intermittently rather than to use very large doses of resin along with a severe restriction of diet. Relative constancy of sodium intake from day to day is essential for satisfactory control of edema. When marked diet fluctuations occur, resin dosage should be adjusted.

In some patients the use of resin has caused a change in intestinal motility. In a few instances a mild diarrhea has developed, in others, constipation. The latter has been easily controlled by the use of a bulk laxative such as methyl cellulose. No instances of fecal impaction have been encountered.

Two typical examples of the striking improvement observed in this study are contained in the following case reports:

C. W. (No. 256894), a white man, age 35, was known to have had rheumatic heart disease for at least 20 years. The first evidence of congestive heart failure appeared in March of 1949 and was controlled by the usual cardiac regimen. In August, 1950, the patient was admitted to the hospital for a trial on ion exchange resin since a diet of 1.5 Gm. of sodium,

maintenance dosage of digitoxin, and 2 cc. of a mercurial diuretic twice weekly had not controlled his edema. Embolic phenomena made necessary the continuous use of anticoagulant therapy. On a dosage of 60 Gm. of resin per day and a 3 Gm. sodium diet it was possible to maintain the patient free of edema for the subsequent nine months. In May of 1951 resin was discontinued for a period of six days during which there was a gain of 7 pounds in spite of three injections of a mercurial diuretic.

M. W. (No. 261255), a white man, age 68, manifested a marked tendency for ascites formation due to hepatic cirrhosis. Satisfactory control of ascites had been accomplished only by restriction of dietary sodium to 400 mg. per day and administration of a mercurial diuretic three times per week. Attempted lienorenal shunt and portal-caval anastomosis had failed to alter the rate of ascites formation. In the two months following the second operation a total of 64 liters of ascitic fluid had been removed.

Resin administration was started with a dosage of 68 Gm. per day and the dietary sodium was increased to 1 Gm. Abdominal paracentesis was unnecessary for three months. Since release from the hospital the patient's dietary sodium has been increased to approximately 1.5 Gm. necessitating an increase in the resin dosage to 80 Gm. per day. Occasional injection of a mercurial diuretic has been necessary. Liberalization of the protein and caloric content of the diet has resulted in a striking improvement in the patient's nutritional status, and at the present time he is able to do light work.

Discussion

The results presented are interpreted as showing that ion exchange resins afford a practical means of controlling the edema of congestive heart failure and the ascites in many patients with cirrhosis of the liver.

In this study the hydrogen form of the resin has been found to be more palatable, less likely to cause gastrointestinal symptoms, and more efficient by weight than the ammonium salt of the resin. The incidence of acidosis is just as great with the ammonium as with the hydrogen resin, since the ammonium radical is dislodged from the resin in the stomach and converted to urea and is thus not available for combination with anions. Potassium deficiency has been prevented by administering approximately one-third of the cation resin in the potassium form.

The studies presented show that when cation resins and the cation-anion mixture are given in equal doses a greater amount of sodium is removed by the latter in spite of the fact that 12 per cent less cation exchange resin is actually present.

This increase in efficiency of cation resin resulting from the simultaneous administration of anion exchange resin was anticipated on the basis of observations made by industrial chemists. Anion and cation resins are used together in a single deionization column for the removal of electrolytes from water.[21] Use of the mixture results in increased efficiency of both exchangers.

The decrease in acidotic tendency noted with the use of the cation-anion mixture is apparently attributable to the increase in fecal excretion of anions. The anion excretion load of the kidneys is thus lessened. It should be noted, however, that with the mixture used in this study the amount of anion removed in the feces is not equal to the number of cations taken up. In a person with normal renal tubular function, sufficient ammonia is produced to excrete the excess anions and thus prevent significant deviation of the concentration of anions in the blood.

In the treatment of an edematous patient it is important to consider factors other than sodium retention that may contribute to the edema formation. For example, when low serum albumin plays some part in the genesis of ascites or edema formation, removal of sodium by the resins may not completely eliminate the excess fluid from the interstitial space. In fact, as with the use of mercurial diuretics and dietary restriction of sodium, in the presence of hypoproteinemia sufficient sodium may be removed to render the body fluids hypotonic without eliminating the edema. By personal communication two deaths in patients receiving resin have come to our attention. Both had far-advanced liver cirrhosis at the time resin therapy was started; other means of controlling the ascites had failed. Serum albumin in both patients was below the so-called critical level for edema formation. Due to anorexia actual sodium intake was considerably below that prescribed by the physician in charge, and no adjustment had been made in resin dosage. Severe diarrhea was a complication in one of the cases.

Terminally both patients manifested marked sodium deficiency and acidosis.

The average daily dose of Carbo-Resin contains 3 to 4 Gm. of potassium. In patients receiving resin, approximately this amount of potassium is excreted in the urine daily. Obviously in patients in whom oliguria persists after resin therapy has continued for two or three days, there exists the danger of hyperpotassemia.

Long-term studies must be completed before the effect of the continued administration of ion exchange resin on trace elements and the vitamin B complex can be established. No change in the growth curve of rats receiving a diet consisting of 25 per cent cation resin has been observed. No clinical sign of vitamin deficiency or other form of malnutrition has been noted in patients receiving resin for long periods. However, until more evidence is available, a liberal intake of calcium and vitamin B complex is advisable in patients receiving resin continuously for an indefinite time.

In patient 2, table 1, the resin mixture was given with the meals during one three-day period, then between meals during the second period. Fecal analysis revealed no significant difference in sodium uptake.

In some patients, especially children, ingestion of the resin as a suspension in milk rather than water may be preferred. Data on patient 3, table 1, indicate that a slight decrease in sodium uptake probably results from this mode of administration.

Because of their physical characteristics and the relatively bulky dosage, ion exchange resins are not well tolerated by all persons. Further improvement in their form and efficiency is to be expected; this will undoubtedly expand their field of usefulness.

Summary

1. A mixture of 12 per cent anion, 29 per cent potassium and 59 per cent hydrogen resin has been administered continuously for periods of not less than four months to 42 patients with congestive heart failure and to 14 patients with ascites due to cirrhosis of the liver.

2. With this mixture it has been possible to control the edema of congestive heart failure and the ascitic fluid accumulation due to cirrhosis of the liver in patients whose response to conventional therapy, including rigid restriction of sodium and frequent injections of mercurial diuretics, had not been satisfactory.

3. The use of presently available resins is contraindicated in persons with severe impairment of renal tubular function unless frequent laboratory determinations are possible.

4. In patients receiving resin, a potentiation of the effect of mercurial diuretics has been observed.

5. By the addition of anion-exchange resin to the cation exchanger it has been possible to increase the sodium-removing capacity of the resin by almost one-third. This addition also decreases the incidence of disturbances in acid-base balance.

Acknowledgments

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Studies of Plasma Quinidine Content

III. The Value of Delayed Absorptive Coated Tablets in Oral Quinidine Therapy

By JOHN J. SAMPSON, M.D., HARRY FOREMAN, M.D., AND BERTRAM C. SOLOMON, M.D

Quinidine sulfate, orally administered in tablets coated with a material delaying their absorption, produces concentration curves in the blood serum similar to those of uncoated tablets. However, there is a delay in the appearance and the attaining of maximum concentrations with the coated tablets, although higher levels may persist for 12 hours. Defects in coating may cause faulty failure of absorption. The advantages of using such a preparation of quinidine are: (1) avoidance of nausea in susceptible persons, (2) providing effective concentrations of the drug during the night and thereby preventing nocturnal attacks of arrhythmias, and (3) providing greater concentrations of the drug in the morning, when attempts at conversions of arrhythmias may require therapy over several days or more.

IN SOME patients the efficacy of quinidine therapy for cardiac arrhythmias is frequently hampered by the accompaniment of nausea, vomiting and, more frequently, by diarrhea. This latter disturbance may occur with doses too small to cause appreciable elevation of the plasma quinidine levels, to 2.0 mg. per liter or above.[1] In the majority of patients nausea and vomiting develop only after sufficient quantity of the drug has been given to produce moderate to high levels of plasma quinidine content, levels over 5 mg. per liter. It is assumed that the gastrointestinal tract is sensitive to the physically irritant effect of the drug in certain individuals, whereas in others the symptoms may be due to neurogenic or other systemic influences.[1] In the first instance it is possible that coating the tablets with material which slowly disintegrates in the gastrointestinal tract may carry the drug beyond the stomach or upper intestines which may be relatively more sensitive to local irritant effects than the lower bowel. It is one of the purposes of this paper to present the effectiveness of such coating* in preventing or diminishing the local irritant effect of quinidine.

Two other uses of delayed absorption of quinidine are suggested, namely (1) the release of the drug at a particular time when its maximum effect is needed, such as in nocturnal paroxysmal arrhythmias, and (2) when prolonged quinidine therapy is required to convert an arrhythmia to a sinus rhythm and awakening the patient at night for medication is undesirable.

The pattern of quinidine absorption has been determined by observing the quinidine content of the plasma after administration of the drug orally in uncoated tablets, rectally in cocoa butter suppositories, and intramuscularly as a solution of quinidine lactate.[1, 3–5] The rate and degree of absorption of quinidine sulfate in "delayed absorptive" coated tablets has not been reported. Rectal administration of quinidine sulfate in cocoa butter suppositories was found previously to give relatively low plasma concentrations of the drug; however, when given to a patient through a colostomy opening in the descending colon, excellent absorption was demonstrated. The plasma quinidine concentration in this patient with a 0.4 Gm. dose of

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This work was supported by a grant from the Eli Lilly Co.

* Enseal Quinidine Sulfate (Lilly), 0.2 Gm. tablets (patented and submitted to American Medical Association Council on Drugs and Therapy for approval) were the coated tablets used.[2]

Similar coatings have been prepared by other manufacturers and depend upon the slow disintegration in a warm, moist medium, such as the contents of the gastrointestinal tract. Enteric-coated capsules or tablets (with salol) dissolve in an alkaline but not an acid medium.

quinidine sulfate in a cocoa butter suppository was 3.6 mg. per liter three hours, and 2.9 mg. per liter five hours after insertion. Thus, it may be assumed that if dissolution of the enteric-coated tablets is delayed until they have reached even this level of the intestine, adequate therapeutic results could be attained.

The plasma quinidine concentrations were determined, using the method of Brodie and Udenfriend,[6] after administering 0.2 Gm. enteric-coated tablets to seven subjects in doses of 0.6 Gm. and 0.8 Gm. (table 1). In this series of subjects minute amounts of quinidine were present in the plasma in two individuals in one and one-half to two hours after administration; appreciable amounts were detected in all but one in two and one-half to three hours and maximum concentration was reached at five hours in three patients; at eight hours in two; and at the final 12 hour period in two subjects. Approximately similar results were obtained with both 0.6 and 0.8 Gm. doses. The variation in the time elapsed before maximum plasma concentration was observed suggests individual differences in the rate and effectiveness of absorption of the drug, with, however, significant maximum quinidine levels of 2.3 to 3.3 mg. per liter in all subjects. These are comparable to the maximum levels obtained with uncoated quinidine sulfate tablets given orally or with intramuscular quinidine lactate, although appearances of peak levels are materially delayed.[1] In all instances, the 12 hour concentration was at least 66 per cent of the quinidine content of the plasma at its peak. As would be expected with delay in absorption, no quinidine was found in the plasma in the one and one-half to two hour specimens, except in two subjects who exhibited minute amounts—due to a technical error in analysis or to more rapid dissolution of the coating on some of the tablets.

TABLE 1.—*Single Dose Administration of Fresh Enteric-Coated Quinidine Sulfate Tablets*

Case	Dose	Plasma Quinidine Content in mg./L. (Hours after Administration)				
		1½-2	2½-3	5	8	12
	Gm.					
1	0.8	0	0.8	2.6	2.0	1.8
2	0.8	0	1.2	3.3	2.8	2.2
3	0.6	0	1.0	3.0	2.7	2.0
4	0.8	0.2	0.5	1.6	2.9	2.8
5	0.8	0	0.9	1.6	2.5	2.4
6	0.8	0.1	0.1	1.4	2.0	2.3
7	0.6	0	0.5	1.3	1.9	2.3

Figure 1 illustrates the curves of quinidine plasma content after single doses of 0.6 Gm. and 0.8 Gm. of quinidine sulfate in coated tablets in seven subjects referred to in table 1.

The tablets were used in these seven subjects within one month of their receipt from the pharamaceutical firm but similar evidence of adequate absorption was obtained on tests on this lot of tablets six months and one year after storage in original bottle containers. This is in contrast to an earlier lot which showed decreasing evidence of absorption after storage for six months, at which time seven out of nine subjects failed to show quinidine in the plasma at any time up to 12 hours after administration. Undissolved tablets were found in the stools of two of these subjects. This indicates that imperfect dissolution through changes in the compression or coating may not become evident until after prolonged storage. Such inadequate absorption of enteric-coated tablets has been previously reported[7] and assurance must be obtained from the pharmaceutical firms that compression and coating of lots of tablets will produce uniformly satisfactory results after storage.

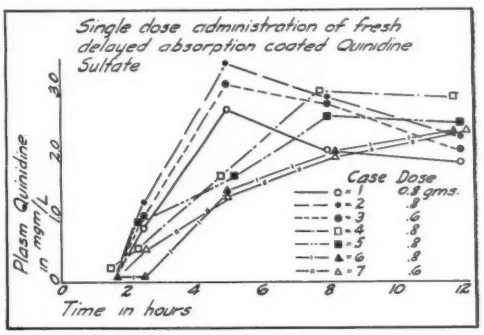


FIGURE 1

As will be mentioned later, certain patients, on whom the drug in coated tablets was used

to prevent or correct an arrhythmia, failed to exhibit any therapeutic effect. Whereas quinidine blood levels were obtained on most of these patients and showed expected concentrations, others were not so studied and could represent faulty absorption.

In order to obtain higher levels of plasma quinidine concentration, multiple doses of from 0.4 Gm. to 0.8 Gm. were given to six individuals (table 2). It will be noted that in four of these, where determinations were made 12 to 14 hours after the last dose, the plasma quinidine content at such times was always over 50 per cent of the maximum concentration obtained. In previous studies of the effects of quinidine administered orally in uncoated tablets the quinidine content in the plasma after 12 hours invariably was between 10 per cent and 30 per cent of the maximum concentration obtained.

The maximum concentrations, namely from 4.7 to 12.8 mg. per liter, attained from the total dosages during the day of 2.4 Gm. to 3.2 Gm. compared favorably with those observed after similar dosage with uncoated quinidine sulfate tablets.

Figure 2 illustrates the curve of plasma quinidine concentration in L. S. (case 12, table 2), a normal male, age 72 years, during and following the administration of 0.4 Gm. of quinidine sulfate in coated tablets every two hours for eight doses. Although the maximum plasma quinidine concentration of 10.6 mg. per liter was obtained 15 hours after the initial dose, the residual concentration 12 hours after the last dose was more than 70 per cent of the maximum concentration observed. A similar example of high quinidine content in the blood 12 hours after the last dose of the drug in coated tablets is given in case 8 (fig. 3), to be discussed later. Thus, in multiple, as in single doses, the delay of the peak concentration and the decreased loss by 12 hours is demonstrated and confirms this rationale for use of such coated tablets clinically.

The coated quinidine sulfate tablets were given to 19 patients; eight with paroxysmal auricular tachycardia; two with paroxysmal ventricular tachycardia, one of whom had persistent ventricular ectopic beats; one with paroxysmal auricular flutter, and two with paroxysmal auricular fibrillation; four with auricular fibrillation; and two with showers of ventricular ectopic beats and sinus rhythm. Of the 10 cases of paroxysmal tachycardia, three were diagnosed as auricular in origin from their clinical response to carotid sinus pressure and the constancy of rate. The other diagnoses were confirmed by electrocardiograms.

In our experience paroxysmal tachycardia

TABLE 2.—*Multiple Oral Doses of Enteric-Coated Quinidine Sulfate Tablets*

Case	Sex	Age	Diagnosis	Dose	Plasma Quinidine Content in mg./L.					
					Hours after first dose					Hours after last dose
					2½–3	4–4½	5–5½	8	12–16	12–14
8. E. F.	F	20	Normal	0.4 q̄ 2° x 7	—	2.0	3.5	4.8	8.8	4.8
9. O. H.	M	67	Art. Ht. Dis., Aur. Fib.	0.4 q̄ 3° x 7	0.7	—	—	—	4.7	3.7
10. F. J.	F	25	Normal	0.4 q̄ 2° x 7	—	—	2.6	5.4	5.8	—
11. R. O.	M	70	Art. Ht. Dis., Aur. Fib.	0.6 q̄ 2° x 4	0.9	—	—	—	12.8	6.8
12. L. S.	M	73	Normal	0.4 q̄ 2° x 8	0.6	—	2.2	9.8	10.6	7.8
13. G. S.	M	50	Rh. Ht. Dis., Aur. Fib.	0.8 q̄ 2° x 4	0.9	2.3	—	8.2	—	—

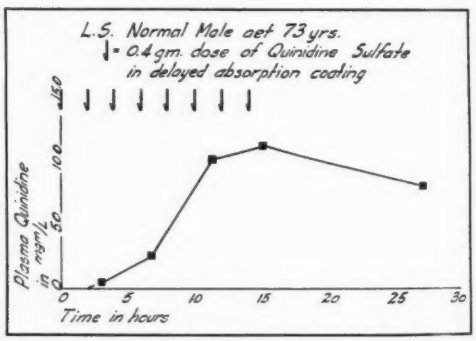


FIGURE 2

frequently occurs late at night or in the early morning although not exclusively so in most patients. Two of the patients with paroxysmal auricular tachycardia had attacks between 4 a.m. and 6 a.m. on three to five nights weekly prior to therapy. In one of the patients, the quinidine therapy abolished the attacks after three months of such recurrence, and in the other, their frequency was reduced to once every one or two weeks after a six week period of frequent episodes.

Ten of 19 patients had experienced prompt nausea and/or diarrhea with small doses of the uncoated tablets, and an eleventh, case 13, severe vomiting and diarrhea after 12 doses of 0.8 Gm. in two days which had failed to convert auricular fibrillation to sinus rhythm. This patient was able to tolerate 18 doses of 0.8 Gm. of quinidine sulfate in coated tablets in two days with only minor nausea and diarrhea, but still retained the auricular fibrillation. Of the 10 other patients who had experienced prompt gastrointestinal sensitivity to uncoated quinidine, seven tolerated therapeutic doses of the drug when coated. In three of these seven, although nausea was prevented, moderate diarrhea still occurred, and in another three individuals with diarrhea but no nausea the coated drug was not significantly different in its effect than the uncoated tablets. No case of nausea followed the use of coated tablets in doses under 2.0 Gm. per day.

Figure 3 illustrates the occurrence of nausea in a normal female (case 8) at a much lower quinidine plasma concentration when uncoated tablets were given than when coated tablets were used.

There were 10 patients in whom delayed absorption was desired to control frequent nocturnal or early morning attacks of paroxysmal arrhythmia. Five of these patients also exhibited gastrointestinal tract irritability and are included in the summary of that group previously mentioned. Six of these 10 patients were definitely relieved of the recurrences of the arrhythmias, although all six were also given uncoated quinidine tablets during the day and in 0.4 Gm. doses in the evening simultaneously with 0.4 Gm. of the coated medication. Four had previously continued to exhibit late nocturnal or early morning arrhythmias when uncoated quinidine alone had been given in similar dosage during the day and at bedtime.

In four patients with persistent auricular fibrillation an attempt was made to shorten the course of quinidine therapy necessary to correct the arrhythmia by giving a dose of the coated drug at night to attain a relatively high plasma quinidine concentration on the next morning. This effect could be anticipated from the data presented in tables 1 and 2. The arrhythmia in one of these patients was converted to sinus rhythm. The three patients whose auricular fibrillation was not converted to sinus rhythm likewise exhibited relatively

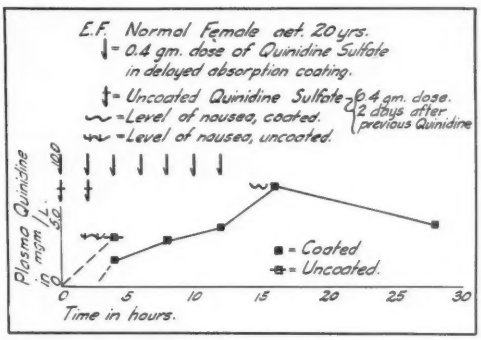


FIGURE 3

high morning plasma quinidine concentrations. This delayed absorption effect obviated the need for disturbing the patient's sleep for nocturnal doses. Nervous tensions accompanying loss of sleep, as well as from other causes, have been noted to increase the refractiveness of certain patients to the conversion of auricular fibrillation to sinus rhythm.

CONCLUSIONS AND SUMMARY

Quinidine sulfate administered in freshly prepared, delayed-absorptive, coated tablets has been shown to produce maximum concentrations in blood plasma similar to those obtained with equal doses of uncoated quinidine.

There is a delay in the appearance of the drug in the plasma, when so administered, of

about two hours and in the maximum concentration of from two to nine hours as compared with the results observed previously with uncoated tablets or capsules.

Imperfect dissolution of the coated tablets was observed in a trial lot after six months storage but not in a recent lot presumably with more perfect coating.

The chief therapeutic values suggested by the use of the coated tablets are:

1. Avoidance of nausea in certain susceptible patients who cannot tolerate even small doses of the ordinary compressed tablets or the powdered drug in gelatin capsules.

2. Utilizing the late development of maximum concentration of the quinidine in the blood to prevent nocturnal or early morning paroxysmal arrhythmias by administering the coated tablets on retiring at night.

3. Shortening the number of days required to convert persistent arrhythmia to sinus rhythm by starting each morning with a higher blood content of quinidine as a result of bedtime doses of the drug in this type of preparation.

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An Etiologic Concept of Atherosclerosis Based on Study of Intimal Alterations after Shock

By O. J. Pollak, M.D., Ph.D.

On the basis of analysis of the bibliography of animal experiments and of anatomic observations on autopsy and surgical material from infants and adolescents who experienced shock, a new concept of atherogenesis is formed. Changes in osmotic pressure, plasmatic dyscolloidity and hypoalbuminemia cause hydropic swelling of the intimal endothelial cells followed by increased permeability. Seepage of plasma through injured endothelium results in edema and hyaline-mucoid change of the subintimal ground substance. Lipoproteins are broken down and most of the foreign matter is resorbed. Lipids, namely cholesterol, remain in the subintima, act as irritants and initiate the alterations known as atherosclerosis.

VOLUMINOUS writing on the histogenesis of atherosclerosis has accumulated. For almost half a century, practically all attention has been focused on lipid deposits in the blood vessels. The reason for this trend lies in the finding of lipid matter in atherosclerotic vessels, namely in atheroma, and in the successful production of atherosclerosis by feeding cholesterol to rodents. A thorough search of the literature leads to a number of articles and notes—often hidden in lengthy German essays—commenting on hyalinosis as preceding lipidosis of the inner layers of arteries. The expression "hyalinosis" is used for want of a better term: the true nature of the protein or protein-like material (albumin, globulin, lipoprotein, glucoprotein, mucoprotein, polyuronide, hyalin, amyloid?) present in the subintimal ground substance is not yet known.

Edema of the inner layers of the vascular wall was first observed in 1856, by Virchow.[1] He thought that the bulging of the intima is due to increased cell size caused by intracellular edema. Twenty years later, Koester[2] and Trompetter[3] described edema (*Quellung*) of the intimal ground substance. They assumed that the fluid arrived in the intima through the vasa vasorum. (The older authors did not differentiate between intima and subintima but spoke of superficial and of deep layers of the intima, respectively.) Voigts[4] stated that mucoid quelling or hyaline degeneration was a common finding in human blood vessels. Torhorst[5] discussed "mucinosis" of the pulmonary arteries. He was the first to hint that the material deposited in the intima might originate from the blood stream.

On the basis of these reports, a discussion ensued about whether or not edema and mucoid change of the intima precede lipidosis. Ribbert[6] gave the sequence of events as follows: (a) increased blood pressure, (b) imbibition by the vessel wall of plasma through pressure, (c) precipitation of proteins, (d) drainage of fluid by lymphatics, and (e) fatty metamorphosis to follow the hyalinosis. Aschoff[7–9] subscribed to the theory of imbibition of lipids. He thought that hyalinosis and lipidosis develop simultaneously because blood plasma contains proteins as well as fats. Rössle[10] objected to the concept of imbibition (*Einpressen*) of lipids. He claimed that penetration (*Eindringen*) of proteins initiates the vascular damage. Schürmann and MacMahon[11] studied extensively the nosogenesis of malignant nephrosclerosis. They chose the term "dysoria" to explain functional damage to the endothelial blood-tissue barrier with subsequent increase in subendothelial mucoid ground substance of renal arterioles and capillaries. More recently, Meyer[12] applied the term "plasmapheresis" to characterize the process by which plasma seeps through a supposedly intact endothelium into the subintimal layer of the aorta. He compared the process to the formation of an

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exudate, or rather insudate, in which fine molecular noncoagulable protein particles are dispersed. Unfortunately, Meyer reverts to Virchow's misconception that edema is always indicative of inflammation. Virchow[1] spoke of "chronic deforming endarteritis"; Meyer[12] concluded that "atherosclerosis is a reactive, productive, inflammatory, chronic process with tendency to recurrence." Certainly, atherosclerosis can develop on the basis of inflammation, arteritis. But this is an exception and not the rule.

Edema and hyaline-mucoid alterations are seen as elevated, white or pale yellow streaks and patches upon the cusps of the mitral valve, in the aorta and also in smaller vessels of children and young adults. They may be present in the inferior vena cava. The impression that such alterations are absent or rare in adults is erroneous. It is due to the fact that pathologists are satisfied with gross observations and only seldom study microscopically the intimal patches. The alterations are easily missed unless one examines a multitude of gross lesions which differ but slightly in appearance and selects also seemingly normal sectors of various blood vessels for histologic study.

The discussion as to whether juvenile and senile plaques are fundamentally different or whether they are part of the same disease process has not yet been closed. Stumpf[13] examined 84 aortas: 35 from babies less than a year old, 35 from children below 15 years, and 14 from juveniles less than 20 years old. He observed in over one-half of all vessels gross patching of the aorta and, microscopically, loosening of the ground substance of the intima. About two-thirds of his patients had died of chronic infections and about one-third of the children with aortic lesions had died of acute infections. He held chronic infection to be the causative factor for vascular changes. From the study of aortas from 644 persons below the age of 16 years, Schmidtmann[14] arrived at a similar conclusion but singled out tuberculosis as an etiologic factor. Zinserling[15, 16] described hyalinosis, lipidosis and calcinosis in the aorta of 12 persons aged from 14 to 36 years. He found[15] analogous lesions in the aorta of dogs. The three phenomena were held to be independent.[16] Hueck[17] disagreed as to etiology; he accused chronic infectious-inflammatory diseases rather than acute ones. He also objected[18] to usage of the term "degeneration" because mucoid change—the basis for all disease processes—is not a change of the vascular tissue in the sense of metamorphosis but represents the result of penetration of blood plasma into the intima. Saltykow[19] surveyed the literature referring to atherosclerosis in youth. He charted the per cent incidence of varying stages of atherosclerosis in the various age groups. The frequency of lesions was six times higher in children deceased of infectious diseases than in children who had died of other causes. Tuberculosis was the cause of death in 73 children while other infectious diseases caused the death of 42 children in whom aortic lesions were found.

Holle[20] described subintimal edema with or without lipidosis in a 27 year old man who died of pneumonia within four weeks, in a 19 year old boy who died within two days of an influenza-pneumonia, in a 20 year old boy who succumbed to meningococcus-meningitis within a single day, and in a 28 year old man who expired within a few hours after rupture of a cerebral hemangioma. Martius[21] studied the mitral valves of children. He saw atherosclerotic patches in 54 (32 per cent) of 178 patients who died of infectious diseases. No such lesions were found in 62 children with syphilis or tuberculosis and in 48 children who had died of malnutrition. However, of 28 patients deceased of miscellaneous causes, three had plaques and of these three two had died of third degree burns and one of carbon monoxide intoxication.

Mucoid vascular lesions are not confined to youth. Rössle[10] observed edematous intimal cushions in 5 per cent of all persons, at necropsy. Among persons with gross atherosclerosis, 10 per cent had the hyaline type of lesions. Meyer[12] saw grossly intimal edematous blebs in the aorta of 5 per cent of 22 middle aged persons with atherosclerosis and corresponding microscopic alterations in 100 per cent.

One of the reasons why many a controversial question has not yet been solved lies in the fact that almost all studies concern themselves with the aorta. Little attention has been paid to the

visceral vessels. Recently, Baker and Selikoff[22] demonstrated cholesterol in hyalinized renal arterioles. Similar results might be expected from study of cerebral and splenic vessels. Hyalinosis seems to precede the deposit of lipids, regardless of the caliber of the diseased blood vessel. The etiology of alterations of various vessels seems also to be the same. Schürmann and MacMahon[12] mentioned a great number of bacterial, serologic and inorganic toxins as possible damaging agents of renal capillaries and arterioles.

The theory that bacterial toxins play a role in the development of atherosclerosis received support from experimental data. Klotz[23] produced noninflammatory intimal lesions by intravenous injection of typhoid bacteria. Saltykow[24, 25] injected rabbits with cultures of staphylococci and produced alterations in the aorta and large vessels. He believed that mucoid matter is formed locally, within the vessel wall. Anitschkow,[26] from observations on rabbits, arrived at the conclusion that mucoid matter enters the vessels from the blood stream, together with lipids. Rinehart and Greenberg[27] pointed out the similarities of mucoid intimal alterations in pyridoxine deficient monkeys and in juvenile human atherosclerosis. Rinehart and Abul-Haj[28] identified abundant mucopolysaccharides in the subintima, by histochemical reactions.

Many of the conclusions reached by the investigators whose works were cited above are equivocal. Their observations are, by and large, correct. Illustrations in many of the quoted papers are inferior and lack details. Thus, it is, for example, impossible to check on Meyer's[12] impression that the intimal endothelium covering a mucoid aortic defect is intact. Still, clarification of this particular question is of utmost importance for the understanding of atherogenesis.

Material and Methods

In performing necropsies on children and adolescents, we gained the impression that atherosclerotic plaques are more common and more numerous in youngsters who had died suddenly or after only a brief hospital stay than in other groups of juveniles. (Patients with lipid nephrosis form an exception.) Many of the young people who had been well prior to terminal hospitalization had grossly visible plaques in the aorta and in other blood vessels, as well.

These observations prompted a careful review of case histories, necropsy protocols, reports on surgical specimens and of tissue sections. Only such postmortem material was selected for this study when necropsy was performed within three hours after death. In many instances, additional tissue blocks were processed and special stains for mucin, neutral fat and cholesterol were applied.

Slides from 96 consecutive necropsies on patients aged from 6 weeks to 22 years were studied. Among these patients there were 31 who had died either from violence or unexpectedly. They were between 9 weeks and 22 years old. Tissues removed from 13 young patients who experienced shock, for example, due to perforation of the appendix, were examined. This surgical material was compared with 60 analogous specimens removed under less dramatic conditions. In both groups, the youngest patient was $4\frac{1}{2}$ months old and the oldest was 23 years. Finally, the large vessels and organs of 21 patients aged between 60 and 95 years were searched for comparable vascular alterations. These patients had died from various ailments but all had experienced terminal traumatism, such as a major surgical operation, or shock, for example, from paralytic ileus. All these old persons had clinical and anatomic evidence of marked atherosclerosis.

Observations

To avoid tedious abstracts of case histories and repetitious descriptions of gross and microscopic observations, six representative cases are hereby illustrated. Cases 1, 2, and 3 form a sequence depicting the evolution of vascular alterations. Case 4 is shown as an example of comparable histologic findings in surgical specimens and also to counteract the argument that disruption of the intimal endothelium might be a postmortem change. (Where such is the case, the endothelium, or large portions of it, is lifted up in toto and not individual endothelial cells.) Cases 5 and 6 are presented to support the

statement that vascular lesions in the young and old have basically the same character.

Case 1. A 9 week old baby (R. S.) fell from a high bed two and one-half hours before admission. The child was dead on arrival at the hospital and necropsy (A-50-108) was performed promptly. The baby was well developed and normally nourished.



FIG. 1. Aorta (× 130) of case 1. Severe laceration of the intimal endothelium. Disruption of the cell membranes, loss of nuclei of the endothelial cells. Intracellular edema. Interstitial edema of the subintimal ground substance. Increased metachromasia (by special stains) of the edematous tissues. Positive reactions for fat and for cholesterol (by special stains) confined to the edematous areas. The edema stops at the media. (Intimal-subintimal layer is rather narrow in an infant of this age.)

It had been well up to the time of the accident. Extensive bilateral subarachnoidal hemorrhage with molding of the brain was found at autopsy. Grossly, the aorta appeared normal. Microscopically, vascular lesions were present in the aorta, periaortic artery, pulmonary and bronchial arteries. Lesions might have been present in other visceral vessels but were not found in the sections viewed. (See figs. 1 and 2.)

Case 2. A 15 year old boy (W. M.) was pinned against the wall of a house by an automobile backing out of a garage. The boy was riding a bycycle. He was taken to the hospital, infused with plasma and whole blood; his wounds were treated surgically. He died 23 hours after admission and autopsy (A-50-110) was performed two hours after death. Numerous, extensive lacerations of the perineum, the scrotum, urinary bladder, multiple compound fractures of the pelvis and both legs, and severe pulmonary edema were found on necropsy. Numerous plaques were present in the ascending aorta, even more in the abdominal aorta, and also in the inferior vena cava. Microscopically, alterations were



FIG. 2. Periaortic artery (× 550) of case 1. Hydropic swelling of endothelial cells. Adventitial edema.

seen in the aorta, vena cava, and in pulmonary arteries. (See figs. 3, 4, and 5.)

Case 3. A 22 year old woman (C. D.) died during labor from excessive blood loss due to fibrinogenopenia. This primigravid, primiparous woman received infusion of 500 cc. of plasma and transfusion of 3000 cc. of whole blood. (Fibrinogen was not available.) The patient had been well before and during pregnancy. Necropsy (A-50-29) was performed two and one-half hours after death. The pertinent findings were severe anemia, generalized visceral edema, and terminal infarction of the myocardial septum due to anoxia. Numerous plaques were present throughout the aorta. The microscopic picture of the

vascular lesions differed from that of other patients in the series: the process was more advanced. (See fig. 6.)

Case 4. A 4¼ year old girl (R. M.) experienced rupture of a gangrenous appendix. At surgical operation performed 19 hours after perforation, localized peritonitis was found. Recovery from shock and operation was uneventful. Examination of the surgical specimen (SJ-51-43) confirmed the clinical diagnosis. Microscopically, alterations were seen in a periappendiceal artery. (See fig. 7.)

Similar alterations were found in the vast majority of appendixes with perforation. The oldest patient in this group was a 23 year old woman. Her appendix was removed 24 hours after perforation. There was prolonged shock and recovery was slow. Hydropic swelling was present in several arteries within the appendiceal serosa.



FIG. 3. Aorta (× 130) of case 2. Intra- and extracellular edema of the subintima. Sphering of nuclei in the upper layers, loss of nuclei. Loss of collagen and disorganization of hyaline trabeculae. Increased metachromasia of the ground substance. Neutral fat (sudanophilic granules) present in the upper layers of the subintima. Cholesterol (giving a positive Schultz' reaction) in fine and coarse granules, also mostly in the upper subintimal layers. No cholesterol esters present (negative polarization). Alterations stop at the media.

Case 5. A 19 year old boy (W. R.) fell backward on the roller-skating rink, three days prior to admission and five days before death. He had been well until the accident. He was admitted with headache and vomiting, became unconscious and developed convulsions. On admission, his cerebrospinal fluid was bloody. His total blood cholesterol equaled only 80 mg. per 100 cc., and the ratio of free to total cholesterol was normal, determined by the Schoenheimer-Sperry method. At necropsy (A-49-43), the salient findings were excessive cerebral hemorrhage, internal hemocephalus, subarachnoidal hemorrhage, and pulmonary edema. Numerous plaques were present throughout the aorta and in the coronary arteries. [See figs. 8 and 9 (to be compared with fig. 10).]

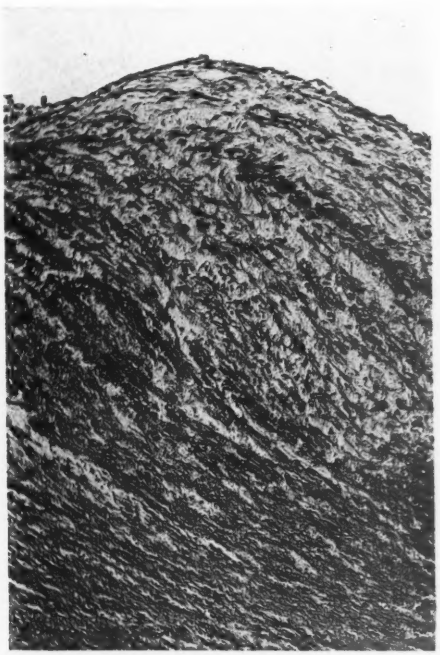


FIG. 4. Inferior vena cava (× 115) of case 2. Section through intimal cushion. Marked interstitial edema, loss of cellularity, disappearance of elastic fibers, hyalinization of the ground substance. Metachromasia is prominent; the reactions for neutral fat and for cholesterol are moderately positive.

Case 6. A 65 year old man (T. G.) experienced a cerebrovascular accident at the age of 59. Atherosclerosis was diagnosed clinically and confirmed by ophthalmoscopy. For about a year, the patient had had complaints which, on his first visit to the clinic, prompted study for esophageal carcinoma. The diagnosis of gastric adenocarcinoma, grade III, was

made from esophageal biopsy. The patient died three days after surgical exploration. His total blood cholesterol was 180 mg. per 100 cc.; the ratio of free to esterified cholesterol was normal. At necropsy (A-51-47), extensive gastric carcinoma involving the proximal half of the stomach was found. The neoplasm extended subepithelially to the esophagus and had metastasized to the liver and the regional lymph nodes. There was severe generalized atherosclerosis. (See fig. 10.)

Figure 10, compared with figure 9, shows less metachromasia, more severe sudanophilia, about an equal amount of cholesterol, no polarizing material in either aorta. There is greater loss of cells and there is intense neoformation of connective tissue fibers. Demarcation of alterations against the media is not as sharp. Still, basically, the histologic picture is the same as that of "juvenile" atherosclerosis.

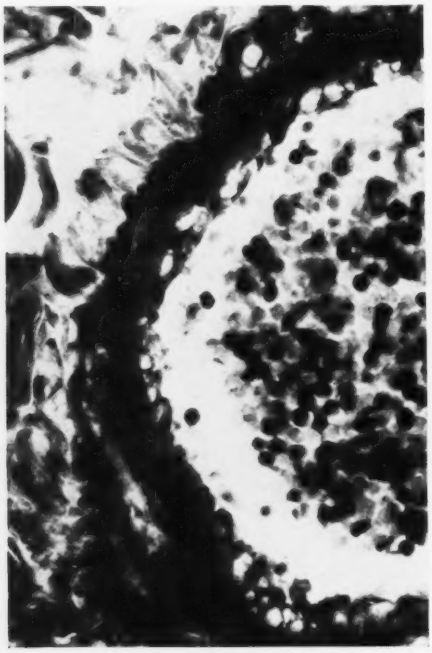


FIG. 5. Pulmonary artery (× 550) of case 2. Hydropic swelling of intimal endothelial cells. (Pulmonary edema).

DISCUSSION

Gross and/or microscopic vascular alterations were found in all our patients who had experienced shock. Of the many investigators[13–21] who described juvenile atherosclerosis but two[20, 21] reported aortic and mitral plaques in young persons who died after brief illness and in children who died of burns or of intoxication. Most authors named acute or chronic infectious diseases, namely tuberculosis, as atherogenic. Our investigation did not include patients who died of infections. Thanks to medical progress, little material is available for such study. If contagious diseases were responsible for initial vascular damage the incidence of atherosclerosis should steadily diminish. On the other hand, bacterial toxins were successfully used to produce intimal alterations in animals.[23–25] A common denominator was found by Selye[29] who classified trauma, hemorrhage, burns, infections and many other factors as "alarming stimuli."



FIG. 6. Aorta (× 113) of case 3. Disruption of cell membranes of the endothelial cells. Edema of these cells, sphering of nuclei. Abundant neutral fat, free cholesterol and cholesterol esters (positive polarization), the latter intracellularly, only. Large, polyhedral lipophages seated mostly in the deeper layers of the subintima, but some located in the superficial layers, just beneath the intima. The amount of esterified cholesterol smaller than amount of free cholesterol. Newly formed connective tissue fibers in the deepest layer of the subintima.

In no single person who had died without having been exposed to shock were comparable vascular alterations found, in our series. In none of the surgical specimens removed were the blood vessels altered except in those of patients who had experienced severe or prolonged shock. The dividing line between the two groups of patients was clear-cut.

The importance of studying visceral vessels microscopically and of examining sections from various sectors of large vessels must be stressed. Frequently, hydropic swelling of the intimal endothelial cells of arterioles and small arteries represents the only abnormal finding. Of course, the thickness of the subintima of these vessels is negligible in comparison with that of the aorta and therefore edema and hyalinosis is not as impressive in the visceral vessels as in the aorta or vena cava. For similar reasons, comparison of experimental atherosclerosis in rodents with human atherosclerosis is difficult. In animals, hydropic swelling of the intima results, according to Pollak and Wadler,[30] promptly on intravascular injection of cholesterol sols. Pollak[31] found desoxycholic acid in small doses extremely damaging to the vascular intima of rabbits. Beneath such damaged endothelium there is increased metachromasia and, directly underneath the lesion, a varying amount of material can be demonstrated which gives positive staining reactions for neutral fat and for cholesterol. Schmitt[32] performed a series of significant experiments. He succeeded in producing cholesterol atheromatosis in rabbits with very small doses, if the vessels were previously damaged by repeated injection of foreign protein. After injection of hog serum, daily feeding of 0.4 Gm. of cholesterol for but three days (total dose, 1.2 Gm.) resulted in aortic lesions. Such a dose is ineffective in noninjected control rabbits. Bevans, Davidson and Abell[33] lately mentioned irregularities of the intimal surface, increased hydrostatic pressure, and interruption of the continuity of the vascular lumen as initial atherosclerotic changes in man and in dog. They stated that intimal thickening impedes the free flow and thus disturbs the rather precarious colloidal dispersion of the plasma lipids. They recongized injury to endothelial cells but did not find an answer to the question of its significance. Until now, such injury has been denied by most investigators. In our opinion, hydropic swelling of the intimal endothelial cells with edema, loosening and breakage of their cell membrane, has been largely overlooked, or, where observed, not correlated with atherogenesis. It is significant that such damage is found regularly in human beings and animals upon change in osmotic pressure caused by colloidal-chemical disturbances of the blood plasma. Similar endothelial edema may be seen in histamine shock. Hueck's[18] statement that blood plasma can pass intact "syncytial" endothelium holds true for capillaries and possibly for precapillaries but not for larger vessels. (A discussion of the "protoplasmic" theory against the "cellular" theory would be out of place.)



FIG. 7. Periappendiceal artery (× 550) of case 4. Hydropic swelling of intimal endothelial cells. Adventitial edema. (Compare with figs. 2 and 5.)

Dyscolloidity, disturbance of the osmotic pressure, and increased permeability of capillaries are accepted phenomena of shock. Increased permeability of the endothelium of the

whole vascular system subsequent to injury of the intima seems to be an additional feature of shock.

It might be suggested that plasmatic dyscolloidity as such suffices to produce vascular damage through pressure changes. Anitschkow,[34, 35] Okunoff[36] and Zinserling[15] demonstrated that bile pigment and colloidal dyes injected into the blood stream of various animals appear promptly in the vascular subintima in the same sectors of the aorta in which cholesterol deposits are found upon feeding. The phenomenon has been confirmed by Pollak and Wadler[30] who injected intravascularly colloidal graphite and sodium stearate into rabbits. Hypoalbuminemia of shock represents another factor in the development of vascular damage: it is responsible for the pressure change and it facilitates precipitation of hydrophobic colloids, such as cholesterol. According to Pollak,[37, 38] albumin is the best stabilizer of cholesterol sols.



FIG. 8. Normal sector of aorta (× 130) of case 5. No increase in metachromasia of ground substance; reactions for fat and cholesterol are negative. (Compare with fig. 9.)

Damage to the endothelial cells facilitates seepage of blood plasma into the subintima. This results in intercellular edema and loosening of the ground substance. The process is characterized by increased metachromasia. Sometimes, intimal "cysts" are formed. Intracellular edema causes swelling of the cells. Their nuclei become round, spheric, and later undergo karyolysis and disappear. The edema and hyalinosis causes thickening of the subintima. The edema stops abruptly at the media. Elastic fibers of the lower subintima become fragile and disappear. So do collagen and hyaline trabeculae. In the next phase, the reactive process of the mesenchyme takes place: hyalinosis is followed by neoformation of connective tissue, and at the same time lipophages appear. Then, the intima proper becomes fibrosed and thickened.



FIG. 9. Plaque of aorta (× 130) of case 5. Thickening of the intimal-subintimal layer. There is damage to the endothelium, interstitial edema with "cyst" formation in all layers of the loosened subintimal ground substance. Metachromasia is severe; microchemical reactions for neutral fat and cholesterol are positive. Marked fragmentation of fibers. (Compare with figs. 8 and 10.)

Thus, the initial damage to the endothelium becomes obscured. (Compare fig. 10.) By this time, the plasma has been resorbed and only coarse particles of lipoproteid complexes are left behind. The results of histochemical reactions for neutral fat and for cholesterol which are found extracellularly in exactly the areas which correspond to the imbibition by plasma are held confirmative for our concept. The absence of cholesterol esters can be demonstrated by the lack of polarizing material. This is further supportive evidence. Faber[39] pointed out that a breakdown of lipoproteins in the tissues apparently is due to action of heparin. Cholesterol is first liberated and then locally esterified. Within the lipophages, cholesterol esters can be demonstrated. Cholesterol esters act as a local irritant. They initiate the process known to us as atherosclerosis. The interplay of physicochemical forces and morphologic alterations discussed by us represents the overture to atherosclerosis.

Most recently, Gianni[39–41] arrived at very similar conclusions by using an investigative approach comparable to ours. He studied autopsy material and performed animal experiments with intravascular injection of cholesterol sols. He subscribes to the concept of insudation of plasma which initiates endothelial and mesenchymal subendothelial changes. He recognizes four different types of anatomic alterations depending upon the composition of the effused plasma (plasma poor in protein and lipids causing edema, plasma rich in various lipids initiating atherosclerosis, plasma rich in glucoproteins with subsequent mucinosis, and plasma with abundant fibrin causing fibrinoid degeneration of the inner vascular layers.) This classification seems too hypothetical. Gianni's[41] correlation of the appearance of atherosclerosis after infectious diseases, in neoplastic diseases and in diabetes complicated with infectious disease follows the line of thought of other authors cited.

Physical forces within the blood stream, such as differences in local pressure, and the rate of flow determine the localization of plaques, together with structural factors, such as the elasticity, or the branching of vessels. Anatomic differences between vessels of various caliber and between arteries and veins are largely responsible for the fate of alterations. In the large arteries, the media represents, for a certain period at least, a barrier for the resorption of material deposited in the subintima. The lack of vasa vasorum in the inner layers represents another unfavorable factor for resorption.



FIG. 10. Aorta (× 130) of case 6. Section through plaque. Marked thickening of intima and subintima. Interstitial edema with "cyst" formation. Cysts mostly located in the deeper layers. Severe loss of nuclei. Increased metachromasia; positive stains for fat and cholesterol but no polarizing material seen. Neoformation of connective tissue of subintima and also of the intima proper, the latter obscuring the endothelial layer and any endothelial damage which might have been present before. (Compare with fig. 9.)

Differences in vascularity in various species and in different sectors of the same vessel play a role. Various segments of the aorta as well as of other vessels have to meet different functional requirements. The role of these factors in the development and localization of atheroma, and for the formation and fate of aneurysms has been recognized. A vessel previ-

ously damaged will be more susceptible to repeated insults. Also, repair will be progressively poorer.

Aschoff[7, 8] stated that atherosclerosis is a pathologic process superimposed on a physiologic aging process. He also pointed out[43] that affinity to lipids increases with aging of the blood vessels. Björling[44] studied the morphologic, tinctorial and chemical properties of vascular ground substance. He found an increased metachromasia, that is, an increase in mucoid tissues, in atherosclerotic and syphilitic aortas. Of great interest is the observation of Steinbiss.[45] Medial alterations analogous to those obtained on treatment with epinephrine were produced by feeding animals dried organs. Addition of vegetables to the animal protein diet resulted in marked metachromasia of the lower subintimal layers and in a microscopic picture similar to that of experimental cholesterol atherosclerosis. Schultz[46] proved that metachromasia of the ground substance increases with age but found that this process is greatly enhanced by atherosclerosis. The affinity to lipids increases parallel with metachromasia. Solowjew[47, 48] confirmed these observations. In our study, lipids could be demonstrated only in the atherosclerotic sectors.

Certainly all tissues change with age. There is anatomic and chemical aging. The acidity of tissues increases with age; this favors the precipitation of cholesterol. Throughout life, calcium accumulates in the vascular media. Aging of tissues is reflected in blood chemical changes. With advancing age, there is hypoalbuminemia, relative hyperbetaglobulinemia, a tendency to hypercholesterolemia, a decrease in blood lipase and other enzymes. All these changes are part of the terrain for atherogenesis. Normal aging should therefore be considered in the discussion. Physiologic and pathologic aging can hardly be separated. Oversimplification of the problem of atherosclerosis should be avoided.

The question of identity of juvenile and adult or senile atherosclerosis is closely linked to the question of the degree to which hyaline-mucoid changes are reversible. Hueck[17] thought that the lesions seen in children might, but need not, lead to adult atherosclerosis. Saltykow[49] believed, on the basis of statistics, that juvenile lesions represent the initial stage of adult atherosclerosis. Lubarsch[50] spoke of the identity of alterations in young and old. Schmidtmann[14] subscribed to the same concept because of lack of evidence that juvenile lesions are reversible. Aschoff[42] considered lesions in children reversible but spoke of them as the "presclerotic phase" of atherosclerosis. Our own observations on human and animal material suggest that the fate of initial, that is edematous-hyaline-mucoid alterations depends upon the localization and the extent of the injury and also upon repetition of episodes of dyscolloidity and insults to the blood vessels.

Our concept helps to explain the episodic character of atherosclerosis and the progress of the disease with advancing age. Are we reverting to the abandoned theory of "wear and tear?" The very occurrence of juvenile atherosclerosis repudiates this theory. When we assume that atherosclerogenesis is initiated by "shock" we remain at a safe distance from the "wear and tear" theory. With the usage of the less definitive term "stress" we approach the "wear and tear" theory which implies inevitability of an aging process. Though neither shock nor stress can be entirely avoided, our efforts to mitigate or arrest atherosclerosis need not be futile. We might succeed in strengthening the intimal endothelium. We might attempt to prevent formation of lipoproteid complexes or to break down these molecules. By increasing the serum albumin level, we can stabilize the plasma colloids. We can avoid excessive deposit of irritating material, namely cholesterol, through reduction of the blood cholesterol level. The future might bring other and more effective preventive measures.

Summary

1. A gross and microscopic study of autopsy and surgical specimens from infants, children, adults and from old persons who experienced shock is presented. The observations are compared with material from patients not exposed to shock.

2. In all persons exposed to shock, hydropic

swelling of the intimal endothelial cells of vessels of various caliber was seen.

3. On the basis of an analysis of the bibliography and of original observations, a new concept of the etiology of atherosclerosis is formed.

4. It is being suggested: (a) that physicochemical disturbances of plasma colloids in shock initiate hydropic swelling of the intimal endothelial cells followed by increased permeability; (b) that seepage of plasma through the defective endothelium causes edema and hyaline-mucoid change of the subintima; and (c) that, after the breakdown of lipoproteins and resorption of most of the foreign material, lipids, namely cholesterol, remain in the subintima where they act as irritants and initiate the alterations which are generally known as atherosclerosis.

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The Effects of Intravenous Procaine and Procaine Amide (Pronestyl) upon Ectopic Ventricular Tachycardia Accompanying Acute Myocardial Infarction

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In tests using dogs with ectopic ventricular tachycardia resulting from myocardial infarction, *procaine* has been found to be without practical value as an ectopic impulse suppressor agent. *Procaine amide* has proved to be very effective in reducing the ectopic rate of high frequency tachycardias to low levels, thus eliminating danger of death from the tachycardia. Procaine amide usually does not produce an entirely normal rhythm but this is of little practical importance. The toxicity of procaine amide is relatively low. For approximately equivalent results, in the tachycardias studied, the dosage of procaine amide must be two to three times that of quinidine.

THE DEVELOPMENT of a standard technic for producing rapid ectopic ventricular tachycardia associated with myocardial infarction in dogs[1] has provided a valuable preparation for studies upon the nature and treatment of this kind of arrhythmia.

Comparison of the types of ventricular arrhythmias that develop in association with myocardial infarction in dogs with those found in a large series of patients[2] with myocardial infarction, and comparisons of the reactions of dogs and men exhibiting these ventricular arrhythmias to intravenous quinidine have revealed striking similarities.[3] These similarities appear to justify confidence that results obtained in the dog with myocardial infarction and ectopic ventricular tachycardia can be valuable in deriving principles which would be of value as guides to improvement in the management of patients with ventricular arrhythmias resulting from this cause. Reports from investigations upon the effects of diphenylhydantoin sodium (Dilantin) and phenobarbital,[4] of upper thoracic sympathectomy[5] and of quinidine lactate and gluconate[3] upon ventricular tachycardias produced in this manner have been completed.

The experiments to be reported were planned for the purpose of critically evaluating procaine and procaine amide (Pronestyl) as suppressors of ectopic ventricular tachycardia associated with myocardial infarction. Mautz[6] demonstrated that locally applied procaine, Metycaine, cocaine and potassium chloride significantly increase the electrical threshold for extrasystoles at a constant time in diastole. In another paper[7] Mautz reported that the use of intravenous and locally applied procaine aids in the resuscitation of the heart from ventricular fibrillation by the use of the electric defibrillator and massage. As a result of these studies, the use of procaine prophylactically during surgery in the region of the heart has been recommended.[8]

Wiggers and Wegria have shown that intravenous procaine raises the electrical threshold for ventricular fibrillation produced in dogs by brief direct current stimuli delivered during the vulnerable period.[9] Since ventricular fibrillation is induced by repetitive ectopic impulses, their results obviously were measurements of the relative thresholds for ectopic beats during an unstable stage of repolarization when repetitive

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responses often follow a single effective stimulus.[10] This stage of recovery is characterized by oscillations in excitability.[11]

Procaine has been reported to be effective in preventing ventricular tachycardia and fibrillation in dogs upon administration of a test dose of Adrenalin in the presence of cyclopropane anesthesia.[12–14] These results were not confirmed by Huggins and co-workers in dogs in which ventricular tachycardia and fibrillation were produced by chloroform-epinephrine[15] and cyclopropane-epinephrine[16] technics. Procaine afforded no practical protection against ventricular tachycardia and fibrillation to animals of either series. Experiences with intravenous procaine for the control of arrhythmias during anesthesia in a series of cases reported by Burstein[17] indicate that procaine probably does have value for this purpose, though its duration of action is brief. Zapata Diaz and co-workers[18] terminated auricular paroxysmal tachycardia and ventricular premature systoles by intravenous procaine in a few cases but failed in paroxysmal ventricular tachycardia and in chronic auricular fibrillation.

Procaine amide has recently been found to be effective in protecting dogs against cyclopropane-epinephrine arrhythmias, and in suppressing premature ventricular systoles and ventricular tachycardia in human cardiac patients.[19, 20] Plasma levels decline slowly, about 10 to 20 per cent per hour; therefore long duration of action may be expected. Metabolic changes bring about part of the decrease but the greater part of the procaine amide is excreted in the urine.[19] Procaine amide, used prophylactically, has reduced the incidence and severity of arrhythmias during cyclopropane anesthesia in patients, but did not fully prevent them.[21]

Technics

The preparation of animals and the methods of testing will be described briefly. They have been presented somewhat more completely in previous papers.[1, 3, 4] Under pentobarbital sodium anesthesia (30 mg. per kilogram) and with aseptic surgical precautions the anterior descending artery of the dog is dissected free for a distance sufficient to pass ligatures under it at the level of the free edge of the left auricular appendage. A doubled ligature is then passed under the artery and cut, making two ligatures. A partial occlusion is produced by tying one ligature snugly, but not tightly, around the artery together with a 20 gage hypodermic needle, and withdrawing the needle. The second ligature is tied tightly around the artery after an interval of 30 minutes. By this two stage technic, losses by ventricular fibrillation during the danger period of the first 10 minutes which follows abrupt occlusion are avoided. The chest is closed and the animal is given fluids and other routine postoperative care.

On the following morning, 16 to 20 hours after occlusion and after the animal has completely recovered from anesthesia, a number of control electrocardiograms are made and then testing is begun. At this time the animals characteristically have a rapid ectopic ventricular tachycardia which is persistent and exhibits only minor changes in frequency from hour to hour. If untreated, the ventricular tachycardia continues for two to four days, and in some animals there are ventricular premature beats on the fifth postoperative day. In about 5 to 10 per cent of the animals, the ectopic ventricular activity is not sufficiently rapid or sufficiently constant to be considered suitable for valid testing.

The principal testing is done on the first postoperative day when the ventricular ectopic activity is most intense and most difficult to control. In some animals testing is continued on subsequent days. The term *test* is used to denote all of the doses of the test drug and all procedures and observations performed during any one day of testing.

Effects of morphine in conjunction with procaine and with procaine amide were tested in some experiments. It was found in the earlier study with quinidine compounds that morphine prevented some of the toxic side reactions (vomiting and diarrhea) but did not prevent convulsions. Morphine may have increased the ectopic suppressor effect of quinidine in some experiments.

Results

Procaine

Procaine was used alone in five dogs, and in combination with morphine in four others. In the experiments with procaine alone, doses were 10 or 20 mg. per kilogram, the dose being diluted with Locke's solution to 20 cc. and injected slowly during a period of five minutes. Doses of 10 mg. per kilogram administered at 30-minute intervals until six doses had been given failed to alter significantly the ectopic ventricular frequency. Doses of 20 mg. per kilogram usually produced a quick reduction in ectopic frequency following each dose. The reduction was of brief duration in all cases, usually lasting less than five minutes after the

completion of the injection. Convulsions followed injections in two of the animals.

Procaine following Morphine. Morphine was combined with procaine in five tests upon four

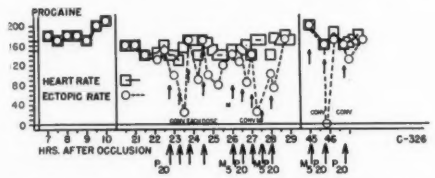


FIG. 1. Effects of procaine, alone and in combination with morphine, administered to a dog with ectopic ventricular tachycardia of moderate frequency. Each arrow designated P_{20} or left unmarked indicates intravenous injection of procaine, 20 mg. per kilogram; M_5, subcutaneous injection of morphine, 5 mg. per kilogram; Conv., convulsions.

animals. The ectopic suppressor effect of procaine was not improved by the addition of morphine, nor were the convulsive reactions prevented.

The chart reproduced in figure 1 serves to illustrate the effects of procaine alone and in combination with large amounts of morphine. The ectopic suppressor effect of procaine (alone) was more evident in this experiment than was usual in the series. The control ectopic rate during the two hours just preceding the first dose of procaine was 130 to 160 per minute, relatively low frequency ventricular tachycardia. The first two doses of procaine (20 mg. per kilogram) produced a marked reduction in ventricular ectopic rate. Before the third dose was administered, however, the ectopic rate had risen to a level higher than that of the control period. Each of the next two doses also produced significant diminutions of ectopic frequency but they were of short duration. Each dose had produced convulsions.

Morphine, 5 mg. per kilogram, was administered subcutaneously one and one-half hours after the fourth dose of procaine. No significant change in ectopic rate occurred in the first 30 minutes after the morphine. Three additional doses of procaine produced effects that were generally similar to the results of procaine administration before morphine, including convulsions. Another dose of morphine was followed by another dose of procaine, but within 30 minutes after the last dose the ectopic rate had risen again to 170 to 180, the highest level of the day.

On the following morning (45 hours post-

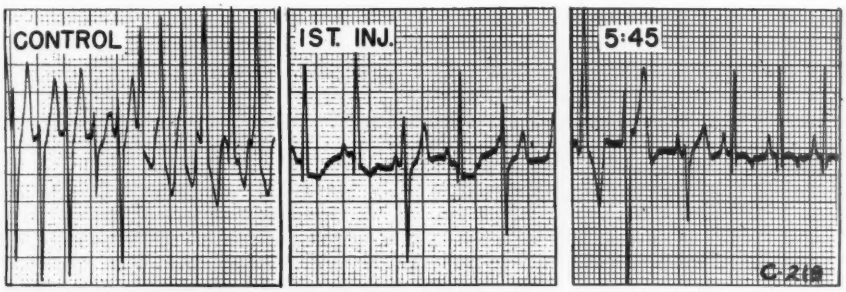


FIG. 2. Electrocardiograms from dog with very high frequency ectopic ventricular tachycardia treated with procaine amide. Description in text.

occlusion) the ectopic rate was 180. Morphine, 5 mg. per kilogram, was injected. This was followed 30 minutes later by procaine. The ectopic rate fell to 0 at the end of the procaine injection, but after five minutes it had risen again to 150, after which it fluctuated between 170 and 190. Another dose of procaine produced a drop to 100 followed by another quick rise to 150 to 170. Each dose was followed by convulsions as before.

In the other experiments, including those in which convulsions did not occur, the ectopic suppressor effects were as feeble and as fleeting as in the one illustrated. It must be concluded that procaine with or without morphine has no practical value as an agent for the suppression of ectopic ventricular tachycardia produced by myocardial infarction.

*Procaine Amide (Pronestyl)**

The effects of procaine amide alone were determined in 12 tests in eight animals. Morphine was administered prior to the first dose of procaine amide in three tests in three animals.

The electrocardiographic results of the administration of procaine amide to an animal with a very high frequency ectopic ventricular tachycardia is illustrated by figure 2. The control record, made on the morning of the first postocclusion day, 18 hours after the operation, shows a ventricular ectopic rate of 300 per minute. Immediately after completion of the five-minute injection of the first dose (40 mg. per kilogram) many beats of normal origin were present and the ectopic rate was reduced to 80 (second record). The third record, made five and three-quarters hours after the first injection, and four hours after the last injection, shows that some ectopic activity still persisted at a safely low frequency along with many normal complexes. The total amount of procaine amide administered was 120 mg. per kilogram.

More complete data from the same experiment was presented in the chart reproduced in figure 3. The administration of procaine amide, 120 mg. per kilogram, during a period of one and three-quarters hours reduced the ectopic rate from 300 to 0. The complete elimination of ectopic complexes lasted for a few minutes only, but the ectopic frequency remained relatively low (10 to 110) without additional doses during the balance of the day of observations, more than nine hours. By the following morning the ectopic rate had risen to 170 and the rhythm again was totally ectopic. An injection of procaine amide, 40 mg. per kilogram, reduced the ectopic activity to a low level during the next 30 minutes, after which it tended to stabilize at a rate of 70 to 80. A second dose had much less effect than the first, and a large increase in ectopic activity began after about 30 minutes. Two later doses produced restlessness and vomiting, and had relatively little ectopic suppressor action. Vomiting was not observed in any other experiment.

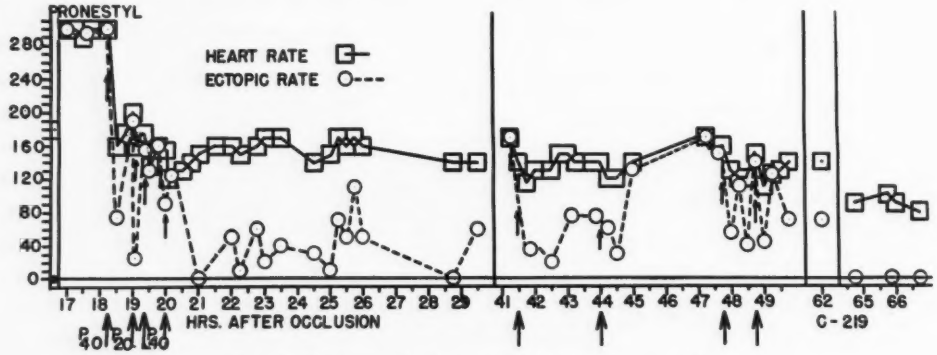


FIG. 3. Chart of animal from which figure 2 was made.

An experiment that showed a somewhat different type of reaction to procaine amide is presented in the chart reproduced in figure 4. The ectopic rate 18 to 19 hours after occlusion was 210 to 230 per minute. The first three doses of procaine amide (each dose 20 mg. per kilogram) at 30-minute intervals reduced the ectopic rate to 0. It remained at 0 to 10 for about 45 minutes, after which there was a quick rise to 140. The second dose reduced the ectopic rate almost to 0 and kept it at a low level for more than an hour after which there was another rising trend. The cycle of increase in ectopic activity and reduction to zero by another dose was repeated two more times at slightly longer intervals.

From the chart in figure 4, it might be expected that additional doses administered at sufficiently short intervals probably would have

* The procaine amide used in this study was generously supplied by E. R. Squibb and Sons.

completely suppressed all ectopic activity. In other experiments, however, in which the elimination of all ectopic activity by large and frequent doses was attempted, low frequency ventricular ectopic rhythms persisted.

Morphine, 5 mg. per kilogram, was administered prior to the first dose of procaine amide in three experiments. Figure 5 is the chart from one of them. On the morning of the first postoperative day, 17 to 18 hours after occlusion, the ectopic rate was 230 to 240. Following the morphine there was a decrease to 210 to 220. The first dose of procaine amide (30 mg. per kilogram) produced a large reduction in ectopic frequency, lowering it to 130. Further doses of equal size at 30 minute intervals produced only small further reductions, though a total of 10 doses of procaine amide were given within six hours. At no time was the ectopic frequency reduced to 0. On the following day two additional doses again reduced the ectopic rate, but not to 0. The use of morphine prior to procaine amide does not appear to have enhanced or impaired its ectopic suppressor action.

An analysis of the results obtained in all the experiments with procaine amide shows that in every test in which a high frequency ectopic ventricular tachycardia existed prior to procaine amide administration, marked reduction of the ectopic frequency was produced. In each of the five animals with ectopic rates from 200 to 300, the ectopic rate was reduced to a relatively low level and maintained at a rate less than one-half of the pretreatment control rate for four hours or longer without toxic symptoms.

In tests with much lower control ectopic rates, the results were less consistent. In the test on the second postocclusion day of an illustrative experiment with a control ectopic frequency fluctuating between 20 and 90, procaine amide, 60 mg. per kilogram (in 20 mg. per kilogram doses) in one and three-quarter hours, made no detectable change in the ectopic rate or the pattern of the fluctuations. In the test on the third postocclusion day on the same animal with a control ectopic rate of 80 to 90 a single dose, 20 mg. per kilogram, eliminated all ectopic activity. There was no return. Other examples of varying results in the suppression of low frequency ectopic ventricular impulses were found in a number of the experiments.

Blood Pressure. Mean blood pressure records were made during three experiments. The pressures were recorded simultaneously with electrocardiograms on a Sanborn Poly-Viso Cardiette, using a Statham gage and carrier-frequency amplifier. The salient observations of the three experiments were as follows:

Experiment C-279. Five doses of procaine amide, 30 mg. per kilogram, two doses, 40 mg.

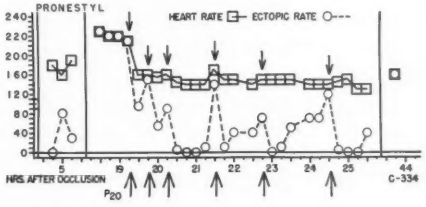


FIG. 4. Procaine amide in another animal. Doses differently distributed.

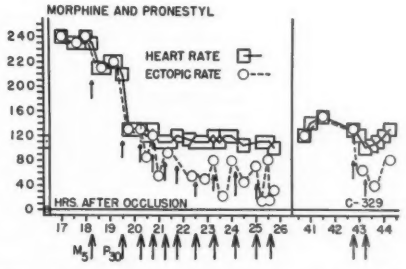


FIG. 5. Morphine and procaine amide. Multiple doses of procaine amide administered in futile attempt to eliminate residual low frequency ectopic impulses.

per kilogram, and one dose, 50 mg. per kilogram, were injected during a period of four and one-half hours. The 30 and 40 mg. per kilogram doses produced reductions of 10 to 20 mm. Hg in mean blood pressure. The control levels were approximately regained between doses, and in some of the intervals the pressure rose to levels higher than the control. The injection of 50 mg. per kilogram 30 minutes after the last 40 mg. per kilogram dose produced a sharp drop of 40 mm. Hg, followed by a slower decline to 0. The sharp drop was accompanied by intraventricular block followed by terminal ventricular fibrillation and death. This experiment

shows that even in a relatively insensitive animal, doses of procaine amide can not be increased indefinitely. In this animal, ectopic activity was never completely eliminated for more than a few minutes at a time.

Experiment C-282. Morphine, 5 mg. per kilogram, was followed after an interval of 45 minutes by the first of five 30 mg. per kilogram doses of procaine amide. These were followed by one 40 mg. per kilogram dose. All doses of procaine amide were given at intervals of 30 minutes. Each dose was followed by a decline of mean blood pressure of 5 to 20 mm. Hg. The animal survived and was in good condition until sacrificed some days later. Low frequency (20 to 50 per minute) ectopic complexes returned between doses, but failed to recur after the last one.

Experiment C-283. Morphine, 5 mg. per kilogram, was followed after an interval of 45 minutes by the first dose of procaine amide. Five doses of equal size, 30 mg. per kilogram, were administered at 30 to 45 minute intervals. After each of the first three doses of procaine amide there was a sharp drop in mean pressure of 20 to 30 mm. Hg, and the control level was not fully regained between doses. The fourth dose produced a fall of 55 mm., from which there was little recovery during the next 30 minutes. The fifth dose was followed by a fall to 0, intraventricular block, terminal ventricular fibrillation and death. This animal was definitely more sensitive to the depressor effects than were the other two.

Study of the protocols does not reveal the cause of the greater vulnerability of this animal. One of the two less sensitive animals also received morphine, 5 mg. per kilogram. The one dog in the entire series that died after the smallest amount of procaine amide (2 doses, 30 mg. per kilogram each) had received no morphine at all. Unfortunately no blood pressure measurements were made on this animal.

Duration of QRS Complexes and of P-R Intervals. In 7 of the 10 dogs, prolongation of the QRS complexes in normally initiated beats was small, remaining below 30 per cent of the control durations throughout the testing procedures. One of these seven dogs with minimal prolongation died after the second 30 mg. per kilogram dose of procaine amide.

Prolongation of QRS by 75 to 100 per cent occurred in three animals. Two of these three animals with a definite prolongation by this amount died.

Variations in the P-R interval bore no relation to dosage or to QRS in seven animals. These included the animal in which failure of the pacemaker and cardiac standstill followed the second dose; the P-R interval was prolonged by no more than 20 per cent (0.10 to 0.12) by the first dose. This is within the limits of spontaneous variation.

There was a significant widening of P-R associated with widening of QRS in the other two fatality cases.

Fatalities. There were three deaths during testing. Widening of the QRS complex sufficient to constitute a warning sign existed prior to the last dose in two animals. In the other case, the animal that died soon after the second dose, the greatest width of QRS after the first dose was 0.05 second compared with 0.04 before treatment.

Study of the protocols of these three animals for other observations that might serve as warning signs revealed only that one dog, the animal most sensitive to procaine amide, was quiet and listless prior to the first dose, and its indifference to surroundings became more pronounced after the first dose was given.

Discussion

Procaine. It has been demonstrated that although intravenous procaine has some ectopic impulse suppressor action, its effective duration is too brief to be of practical value for the treatment of ectopic ventricular tachycardias associated with myocardial infarction. Its tendency to induce convulsions also renders its use in the unanesthetized state objectionable.

Procaine Amide. The experiments have shown that procaine amide is very effective in reducing the frequency of rapid ectopic ventricular tachycardias to relatively low frequency ectopic beats mixed with normal complexes. Usually it has not eliminated all ectopic activity although many additional doses and larger doses were administered after the major

reduction in ectopic frequency had been produced. In some experiments with low frequency ectopic activity prior to the beginning of treatment, procaine amide has had little effect on the ectopic activity. In at least one test with a low ectopic frequency, however, one dose permanently restored a completely normal rhythm. These observations probably signify that two or more factors are active in producing the ectopic activity.[1, 5] In high frequency tachycardia the major factor is antagonized by procaine amide; thus, a reduction of the ectopic frequency to low levels is readily effected. Other factors of relatively minor importance in the production of ectopic impulses apparently are not opposed by procaine amide, but continue to cause low frequency ectopic activity after the major exciting factor has been brought under control. Such minor excitatory factors, refractory to procaine amide, could be the sole or major factor in those low frequency ectopic rhythms that are resistant to this drug.

Clinical Significance. It is well known that in the presence of myocardial infarction a high frequency ectopic ventricular tachycardia is a grave complication. The tachycardia may precipitate ventricular fibrillation[22, 23] or lead to circulatory failure.[2] Fortunately, both of these dire sequelae of rapid ventricular tachycardia can be prevented by reduction of the ectopic frequency to low levels, thereby allowing a favorable proportion of sinus impulses to become effective. With the reduced intensity of ectopic excitatory state in the boundary of the infarct, the danger of an ectopic frequency sufficiently great to produce the conditions required to initiate ventricular fibrillation is effectively nullified.[22, 23] Furthermore, with the slowed rate, diastole has a duration long enough to permit a degree of filling of the ventricles sufficient to provide for effective pumping action.

It is not necessary to stop all ectopic activity to prevent death in these severe ventricular tachycardias, and a determined attempt to do so may prove harmful. Although procaine amide is relatively less toxic than quinidine[3] and certain other drugs used for the control of ventricular ectopic rhythms, it should be remembered that one very quiet animal died after only two doses of procaine amide of a size that was well tolerated in the majority of animals though repeated many times. One other dog died after the administration of an amount of procaine amide that may be regarded as being well within the usual therapeutic range of total dosage during a period of a few hours. The third death occurred only after excessive dosage.

The observations upon two of these dogs suggest that, during treatment of severe ventricular tachycardias with procaine amide, some of the principles which were developed from the observations of the reactions of such dogs to the intravenous administration of quinidine lactate and quinidine gluconate[3] should be applied. In those experiments the animals with hypotension and dyspnea tended to be most sensitive to the drug, and to die after administration of relatively small amounts. In all cases of severe ectopic ventricular tachycardia only that amount of drug which is required to reduce the ectopic rate to a safely low range and to maintain it at a low level should be administered. Eventually the harmless low frequency ectopic beats will cease spontaneously. In all cases of severe ectopic ventricular tachycardia, an electrocardiograph machine, preferably a direct-writing type, should be kept near the patient and used at frequent intervals as a guide to therapy. These experiments indicate that in order to produce equivalent ectopic suppressor effects in ectopic ventricular tachycardias accompanying acute myocardial infarction the dosage of procaine amide should be two to three times that of quinidine lactate or gluconate.[3]

Summary

Procaine, administered intravenously, has a very transient effect in suppressing ectopic impulses in some animals with ectopic ventricular tachycardia, and practically no suppressor effect in others. In some unanesthetized animals, sufficient procaine to exhibit any ectopic suppressor effect induced convulsions. Procaine is of no practical value in such tachycardias.

Procaine amide (Pronestyl) is very effective in reducing the frequency of severe ectopic ventricular tachycardia to safely low levels. Usually

it will not eliminate all ectopic activity, though administered in large and repeated doses. It has yielded variable and unpredictable results in low frequency ectopic rhythms.

It is deduced that in myocardial infarction multiple ectopic excitatory factors probably are active, and that the major factor in high frequency tachycardias is opposed by procaine amide.

The elimination of danger of ventricular fibrillation and a marked improvement in the effectiveness of pumping are achieved by the reduction of the ectopic frequency to low levels. Since such a reduction can be produced by doses of procaine amide that usually produce a little or no toxic reaction, it is regarded as a promising suppressor agent for use in severe ectopic ventricular tachycardias.

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The Electrocardiogram in Heart Disease Detection

A Comparison of the Multiple and Single Lead Procedures

By T. R. Dawber, M.D., W. B. Kannel, M.D., D. E. Love, M.D., and R. B. Streeper, M.D.

In a study of a group of 2000 volunteers in a New England community the authors compare the relative merits of the 12-lead and a simplified lead I electrocardiogram in the detection of heart disease. The contribution the electrocardiograph would make if included in a heart disease screening program is evaluated. A possible heart disease screening method is suggested.

PUBLIC health workers have long been interested in simplified methods for the detection of the chronic diseases. The chest x-ray or photofluorogram has been demonstrated to be an effective means of detecting most chronic pulmonary diseases. Untreated diabetes mellitus may be readily discovered by urine or blood sugar determinations. The blood serologic test remains the ideal method of syphilis case finding. In most other chronic diseases similar detection methods are not available.

In view of the importance of cardiac disease as a cause of chronic disability, the development of a simple method for the recognition of heart abnormalities has been of particular interest.

The possibility that the electrocardiograph might be of value for discovering the presence of heart disease has occurred to many public health workers. The electrocardiograph has been considered an instrument for recording changes in the electrical activity of the heart in persons already suspected of having heart disease and not for the detection of heart disease in the population at large.

While no comparable studies have previously been done to evaluate the electrocardiograph as a screening device for heart disease, several studies have been undertaken in the past to evaluate the electrocardiogram as a routine procedure to be included in the examination of large groups of presumably healthy people. These reports have, for the most part, condemned the procedure as misleading and of little help.

Scrutiny of these studies in the light of present day concepts of electrocardiographic interpretation reveals certain fallacies in the conclusions reached. A study done in 1943 by Vicidi and Geiger on 500 young working adults indicated 50 per cent of the records beyond the limits of "normal."[1] From this the authors concluded that surveys depending on the electrocardiograph as a detection instrument would be misleading unless the criteria used were revised. This conclusion appears justified since 36 per cent of the tracings were considered abnormal solely because of slurring of the QRS complex and an additional 17 per cent were interpreted as abnormal because of a prolonged Q-T interval. Thus about half of their "abnormal" records might be considered within normal limits today.

Another study done on 1812 midshipmen without heart symptoms concluded that the electrocardiogram proved of no help in evaluating the condition of the heart in this group.[2] In this study 48 per cent of the tracings were found to be "abnormal." Analysis of the "abnormalities" reveals such findings as inverted or diphasic T waves in lead III, notched QRS in lead III, left axis deviation, extrasystoles and P-R intervals more than .20 second. By present-day criteria only a few of these would be considered abnormal.

Wood and co-workers, in a study of 229 executives, 153 students selected because of suspected or known heart disease and 705

From the National Heart Institute, National Institutes of Health, U. S. Public Health Service, Federal Security Agency.

unselected students, concluded that, in persons under 30 years of age, the electrocardiogram gave little diagnostic help.[3] In patients with known heart disease it added no further information.

Subsequent study by Graybiel and associates on 1000 young healthy aviators, has set somewhat broader limits of normality in the interpretation of the electrocardiogram.[4] Had these criteria been employed in earlier studies some of the conclusions reached might have been different. Klein and Hess reported on 2000 electrocardiograms in an industrial study.[5] They concluded that the electrocardiogram was a practicable procedure in evaluating the cardiac status of patients in industrial medicine.

In view of the lack of agreement about the value of an electrocardiogram in the detection of heart disease, it was decided that further study of this problem might be worthwhile. It first appeared desirable to assess the value of the multiple lead electrocardiogram as a method of detecting heart disease. However, since it is obviously impracticable to take a complete electrocardiogram for survey purposes, it remained to be determined if a simple record, such as a single lead, could approach the results obtained using the multiple lead record. It also appeared desirable that the records to be evaluated for this purpose should come from a population group similar to that expected in a possible heart disease survey.

Because of the apparent similarity of the persons examined at the Framingham Heart Disease Epidemiology Study to many population groups, it appeared that conclusions reached from a study of this group of individuals would probably be applicable to the population at large.

The Framingham Heart Disease Epidemiology Study is a long term study with biennial follow-up of a large population group. It is primarily concerned with the determination of the factors associated with and contributing to the development of degenerative cardiovascular disease. Five thousand individuals from 20 to 69 years have been studied under this program. A detailed description of the Framingham Study has been presented in detail elsewhere.[6] Of the people examined, 2500 entered as volunteers and, as such, constitute a group generally comparable to other case finding programs depending on volunteer attendance. The material for this study was taken from the records of 2000 of this latter group.

Each individual participating in the Study was assessed by a routine history including present and past symptomatology. This was followed by a physical examination, complete except for pelvic, rectal, otoscopic and neurologic examinations. Blood pressure was taken in both arms initially and repeated on a single arm by a minimum of two additional observers. Temperature, pulse, respiration, and vital capacity were determined by the admitting nurse.

Each person, in addition to the above long work-up, received a short check incorporating a brief history and physical examination, done by one of the regular clinic staff or by a visiting consultant cardiologist.

Laboratory studies which each person received included a chest x-ray, an electrokymogram, a 12-lead electrocardiogram, urinalysis and certain blood studies. When indicated, patients were subjected to fluoroscopy with barium swallow and oblique films. X-ray films were interpreted by consultant radiologists.

The criteria for clinical diagnosis were provided by an advisory committee and are based, with some modifications, on those of the New York Heart Association.[7]

The criteria employed were as follows:

Hypertension

1. If all systolic levels exceeded 159 mm. Hg or all diastolic levels were greater than 95 mm. Hg, a diagnosis of hypertension was made.

2. Blood pressure in the range of 140 to 159 systolic or 90 to 95 diastolic was called borderline hypertension.

3. If, in addition to hypertension as outlined in paragraph 1, there was x-ray evidence of left ventricular enlargement, definite electrocardiographic evidence of left ventricular strain or hypertrophy; or, in instances of both in which no other etiologic factor could be

found, a diagnosis of hypertensive cardiovascular disease was made.

4. History or residua of a cerebrovascular accident in association with hypertension, and in the absence of other etiologic factors, was also considered to be evidence of hypertensive cardiovascular disease.

Coronary Artery Disease

1. Employing the criteria of Harrison and Levine, a diagnosis of coronary artery disease was made in cases of definite angina pectoris.[8, 9] Coronary artery disease was also diagnosed in those cases showing electrocardiographic evidence of myocardial infarction, and in those cases having a history of myocardial infarction in association with nonspecific electrocardiographic changes or with an x-ray film showing an abnormal cardiac silhouette in the absence of other causes, that is, rheumatic, congenital, syphilitic or other diseases. In instances of associated disease such as syphilitic or hypertensive heart disease in which the occurrence of coronary artery disease can be considered a complication rather than the primary disease, the case was classified under the presumed primary disease and does not appear as coronary artery disease.

2. The presence of a tortuous aorta or calcification beyond the ascending aorta was not considered evidence of heart disease.

3. A diagnosis of possible coronary artery disease was made in cases with histories suggestive but not diagnostic of angina pectoris, and in which electrocardiographic changes were absent or nonspecific.

Rheumatic Heart Disease

1. A definitive diagnosis was made when all observers agreed on the presence of murmurs generally considered diagnostic of rheumatic valvular disease.

2. No diagnosis was made in the absence of definitive murmurs. Changes in the cardiac contour were considered confirmatory but not diagnostic.

3. A diagnosis of possible rheumatic heart disease was made in instances of rheumatic history together with systolic murmurs of grade II intensity or less.

4. The term potential rheumatic heart disease was reserved for those having a definite history of rheumatic fever but with no clinical evidence of heart involvement.

Congenital Heart Disease

1. Encountered rarely, congenital heart disease was diagnosed on the basis of generally accepted criteria.

A study was first set up to compare the 12-lead electrocardiogram with the final clinical diagnosis. To establish the electrocardiographic interpretation, each tracing was read by four physicians separately and classified as normal, doubtful or abnormal based on accepted criteria.[10] In instances of disagreement the tracings were reviewed and the majority opinion accepted.

Table 1 shows the comparison between the reading of the multiple lead electrocardiogram and the final clinical impression. It is apparent from this table that the multiple lead electrocardiograph is a fairly reliable instrument in detecting those individuals free of cardiovascular disease, since in 89.3 per cent of individuals free of cardiovascular disease the electrocardiogram was normal beyond the slightest question. In another 7.3 per cent changes of doubtful significance were present. Only 3.4 per cent were interpreted as definitely abnormal. In using the electrocardiograph as a screening instrument it would appear necessary to include the doubtful with the abnormal group, since they would both have to be recalled for further examination. If this were done it is evident that 10.7 per cent of normal individuals would be recalled for further unnecessary examinations.

In patients with definite heart disease or in whom the possibility of heart disease could not be excluded, the value of the electrocardiograph as a detection instrument becomes less apparent, since 53.1 per cent of these with definite heart disease and 64.1 per cent of those with possible heart disease had normal electrocardiograms and would have been missed in any heart disease survey using only the electrocardiograph.

The multiple lead electrocardiogram is

therefore fairly reliable in selecting those persons free of heart disease but misses a high percentage of those with cardiovascular disease.

Although it was not the purpose of this study to compare the relative merits of the various diagnostic methods it is apparent that in hypertensive cardiovascular disease and in rheumatic heart disease, which constituted the bulk of heart disease in this adult population, blood pressure determination and auscultation of the heart would have been better screening devices than the electrocardiogram. However, in coronary artery disease, where 50 per cent were detected by the electrocardiogram, the only other detection method would have been a time consuming history taken by a physician and not suitable for rapid screening purposes.

Having evaluated the multiple lead electrocardiogram an effort was next made to determine the effectiveness of a simplified electrocardiographic tracing as a screening procedure. To be applicable for the purpose intended an abbreviated electrocardiogram must fulfill certain requirements. The record must be simply and quickly obtained and relatively easy to interpret. It must produce results comparable to the multiple-lead electrocardiogram when interpreted only as normal, doubtful or abnormal.

It appeared to the authors that the standard lead I was the single lead which would best fit these requirements. There is a relative constancy of the complexes in lead I in normal individuals. Maroney and Rantz recorded the standard limb leads in 679 healthy infants and children and found that the T wave was never flat, diphasic or inverted in lead I, rarely so in lead II, but frequently so in lead III.[11] Katz states that the T wave is never normally inverted in lead I, except, occasionally, in the upright position.[12] White states that T wave in lead I may be low but that it is always upright normally.[13]

There is a high degree of correlation between

TABLE 1.—*Twelve Leads vs. Final Clinical Impression: 2000 Patient Records*

Final Clinical Impression	Impression from Twelve Leads of ECG							
	Number				Per cent			
	Normal	Doubtful	Abnormal	Total	Normal	Doubtful	Abnormal	Total
No Heart Disease: Total	*1400*	*114*	*53*	*1567*	*89.3*	*7.3*	*3.4*	*100.0*
No cardiovascular disease	981	69	23	1073				
Hypertension	393	42	30	465				
Arteriosclerosis	10	0	0	10				
Other*	16	3	0	19				
Possible Heart Disease: Total	*100*	*32*	*24*	*156*	*64.1*	*20.5*	*15.4*	*100.0*
Possible coronary artery disease	16	10	8	34				
Possible rheumatic heart disease	18	7	3	28				
Other valvular disease	8	0	0	8				
Cardiac hypertrophy only	55	9	3	67				
Heart block only	0	5	9	14				
Other†	3	1	1	5				
Heart Disease: Total	*147*	*51*	*79*	*277*	*53.1*	*18.4*	*28.5*	*100.0*
Hypertensive cardiovascular disease	72	31	51	154				
Coronary artery disease	22	6	16	44				
Rheumatic heart disease	53	12	11	76				
Congenital heart disease	0	2	1	3				

* Includes one or more of each of the following clinical impressions: Raynaud's syndrome, possible heart block, possible paroxysmal auricular tachycardia, possible patent ductus arteriosus, potential rheumatic heart disease, possible rheumatic fever, ectopic auricular rhythm, and cerebral aneurysm.

† Includes one or more of each of the following clinical impressions: possible congenital heart disease, aortitis, pulmonary-cardiac, and possible dilatation of the aorta.

abnormalities in lead I and those demonstrable in the 12-lead electrocardiogram. Riseman and Josephs studied 100 normal patients 45 years old or over and 134 patients with angina pectoris.[14] Of the abnormal electrocardiograms, an inverted, diphasic or absent T wave in

the part of the technician is not essential and the necessary competence can be rapidly attained. Many tests may be done in a short period of time.

A study was therefore set up to determine the value of a single lead I electrocardiogram

TABLE 2.—*Criteria for Lead I*

	Normal	Doubtful	Abnormal
P Wave			
Inverted	0	0	+
Height	Upright, but less than 1.1 mm.	1.1 mm.	0 or over 1.1 mm.
Width	Up to 0.10 second	0.11 second	Over 0.11 second
Contour	—	—	Notched, biphasic, isoelectric
P-R Interval	Less than 0.20 sec.	0.20–0.24 sec.	Over 0.24 sec.
Q Wave			
Width	Less than 0.04 sec.	0.04 sec.	Over 0.04 sec.
Depth	Up to 1.5 mm.	1.5 mm.	Over 1.5 mm.
QRS			
Width	Up to 0.10 sec.	0.11–0.12 sec.	Over 0.12 sec.
R	1.5–12 mm.	12 mm.–20 mm.	Less than 1.5, over 20
S	Less than R.		Equal to or greater than R.
S-T Segment	Less than 1 mm. deviation	1 mm. dev. either way	More than 1 mm. dev.
T Wave			
Inverted	0	0	+
Isoelectric	0	0	+
Biphasic	0	0	+
Amplitude	Above 1 mm. less than 5.5 mm.	1 mm.	Less than 1 mm. more than 5.5
Rate	50–120	50 and 120	Less than 50, more than 120
Rhythm	Normal sinus.		Auricular fibrillation or flutter.
	Sinus Arrythmia.		Ventricular premature beats
			Auricular premature beats
			Par. aur. tachy.
			Par. vent. tachy.
			Complete heart block.
			Wenckebach's phenomenon.

leads I, V_4 and V_5 and V_6 was the combination most frequently encountered. "... In most instances the findings in the standard, precordial, and limb leads corroborated each other." Standard limb leads are the only leads feasible in a large scale survey because of the impracticability of undressing the subjects. Lead I is preferable because it avoids application of electrodes to the lower extremities.

The technic of taking lead I is of sufficient simplicity that a high degree of proficiency on

alone in detecting heart disease. This was carried out in the following manner:

Each of the 2000 multiple lead tracings, already interpreted, was placed in an envelope with an aperture so constructed that only lead I was exposed to inspection. These tracings were then submitted in turn to two readers, who, using criteria as given in table 2, gave independent interpretations, classifying each lead as normal, doubtful, or abnormal. The criteria used were determined arbitrarily

after careful perusal of the literature. It has not been determined that these criteria are necessarily the most desirable. The two readers had a 90 per cent agreement. The remaining tracings were re-read and a common interpretation agreed upon.

Table 3 gives a comparison between the reading of the lead I electrocardiogram and the final clinical impression. It is apparent that there was some loss in the ability of the readers to exclude normal persons since only 80.3 per cent of those individuals free from cardiovascular disease had lead I tracings interpreted as normal. However the ability of lead I to pick up cardiovascular disease appears just as good as the multiple lead procedure. In fact, in terms of absolute numbers, it appeared to be slightly better. This increase in the percentage of abnormals detected was obtained at the expense of a decrease in the per cent of normals excluded and may be explained by the rather rigid criteria used in reading lead I alone. By varying the criteria in re-reading a small group of the lead I tracings it was apparent that the criteria could be adjusted either to exclude more normals or to detect more heart disease but not both.

Having found that lead I, taken in the conventional manner with the patient in the supine position, is almost as effective as the multiple lead electrocardiogram for screening purposes, it remained to be determined if a tracing taken in the upright position, an advantage for screening purposes, was comparable.

Accordingly 12-lead electrocardiograms were taken on 104 patients in the usual manner and an additional lead I was taken with the patient sitting relaxed and holding the paste-covered electrodes between the thumb and forefinger of each hand. It was found that a satisfactory tracing could be so obtained and that no further electrode was needed. When the interpretations of the supine and upright lead I based on criteria in table 2 were compared, it was found that the interpretations agreed in 94 of

TABLE 3.—*Lead I vs. Final Clinical Impression: 2000 Patient Records*

Final Clinical Impression	Impression from Lead I of ECG							
	Number				Per cent			
	Normal	Doubtful	Abnormal	Total	Normal	Doubtful	Abnormal	Total
No Heart Disease: Total	*1259*	*144*	*164*	*1567*	*80.3*	*9.2*	*10.5*	*100.0*
No cardiovascular disease	878	86	109	1073				
Hypertension	357	57	51	465				
Arteriosclerosis	7	1	2	10				
Other*	17	0	2	19				
Possible Heart Disease: Total	*99*	*20*	*37*	*156*	*63.2*	*12.9*	*23.9*	*100.0*
Possible coronary artery disease	17	4	13	34				
Possible rheumatic heart disease	20	3	5	28				
Other valvular disease	6	0	2	8				
Cardiac hypertrophy only	51	6	10	67				
Heart block only	4	5	5	14				
Other†	1	2	2	5				
Heart Disease: Total	*149*	*53*	*84*	*277*	*50.7*	*19.1*	*30.2*	*100.0*
Hypertensive cardiovascular disease	67	39	48	154				
Coronary artery disease	17	4	23	44				
Rheumatic heart disease	54	10	12	76				
Congenital heart disease	2	0	1	3				

* Includes one or more of each of the following clinical impressions: Raynaud's syndrome, possible heart block, possible paroxysmal auricular tachycardia, possible patent ductus arteriosus, potential rheumatic heart disease, possible rheumatic fever, ectopic auricular rhythm, and cerebral aneurysm.

† Includes one or more of each of the following clinical impressions: Possible congenital heart disease, aortitis, pulmonary-cardiac, and possible dilatation of the aorta.

the 104 instances. Of the 10 instances of disagreement, the interpretation based on all 12 leads was taken to be correct. In five of these the reading of the tracing made in the supine position coincided with the interpretation of the 12 lead electrocardiogram. In the remaining five the tracing taken in the upright position proved "correct." This was believed to indicate that there was no essential difference in the reliability of the lead I reading taken in either position.

Summary and Conclusions

1. Previous studies reveal lack of agreement about the value of an electrocardiogram in the detection of heart disease. Data collected on adult volunteers who were examined by the Framingham Heart Disease Epidemiology Study appeared to be ideally suited to study this problem.

2. The completed clinical records of 2,000 such individuals were used to determine the efficiency of the 12 lead electrocardiogram and the single lead I electrocardiogram as mass screening procedures for detecting heart disease.

3. Theoretic and practical reasons for selecting the lead I electrocardiogram are indicated. The criteria used in detecting normal and abnormal lead I electrocardiograms are presented and discussed.

4. The 12-lead electrocardiogram correctly classified 89.3 per cent of the clinically normal persons as normal but incorrectly classified 7.3 per cent as doubtful and 3.4 per cent as abnormal. The 12-lead electrocardiogram incorrectly classified as normal 64.1 per cent of the persons judged by clinical examination to have possible heart disease and incorrectly classified as normal 53.1 per cent of the persons with clinically definite heart disease.

5. The lead I electrocardiogram correctly classified 80.3 per cent of the clinically normal persons as normal but incorrectly classified 9.2 per cent as doubtful and 10.5 per cent as abnormal. The lead I incorrectly classified as normal 63.2 per cent of the persons judged by clinical examination to have possible heart disease and incorrectly classified as normal 50.7 per cent of the persons with clinically definite heart disease.

5. Lead I, with appropriately selected criteria, will correctly classify almost as many normal persons as a 12 lead electrocardiogram. Similarly it will detect essentially the same proportion of persons with clinically definite or possible cardiac abnormalities as the 12-lead electrocardiogram.

7. Either lead I alone or the 12-lead electrocardiogram will fail to classify correctly over half of the persons with clinically definite or possible cardiac disease.

8. A special study on 104 persons showed that there were no important differences in the interpretation of the lead I electrocardiograms in the supine position or the seated position.

9. It is concluded that if the electrocardiogram is to be used for screening, the speed and ease of the technic and the slight loss of efficiency in the use of lead I alone compared with the 12-lead electrocardiogram would appear to make lead I the method of choice for the screening line.

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Vasodilator Effects of a Substance Present in Normal Human Urine in Comparison with the Effect of Methacholine and Sodium Nitrite

A Statistical Analysis of Reliability of the Method of Assay

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This paper presents a method for bioassay of vasotropic substances. Data on the accuracy of the method are presented in terms of the response to repeated injections of methacholine. Some of the factors affecting the response to methacholine are analyzed. The peripheral vasodilator effect of a nondialyzable substance present in human urine is demonstrated and the effectiveness of this substance is related to that of methacholine.

A PREVIOUS paper[3] from this laboratory described the temporary decline in arterial pressure produced by the intravenous injection of a substance present in normal urine. It was suggested that this substance probably acts by causing peripheral vasodilation.[4]* In this paper we describe a method for assaying vasotropic substances by injecting them intra-arterially while recording the venous outflow from the isolated hind limb of the dog. This paper demonstrates by means of this assay technic that the vasodepressor substance in urine has a direct vasodilator effect. The suitability of this method of assay of vasotropic substances is discussed and certain of the factors which lead to variability in the responses to intra-arterial injections are analyzed. This method of assay has the advantage that repeated injections may be made in the same animal and only 0.2 to 0.8 ml. of urine is required whereas 2 to 10 ml. are required when the assay is made by intravenous injections.[3]

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Preliminary reports of this work were presented at the 1948 and 1949 meetings of the American Physiological Society.[1, 2]

During the study, L. T. F. was a fellow of the Life Insurance Medical Research Fund.

* For additional literature on the urinary depressor substance the reader may refer to references 3 and 14 to 16.

METHODS

a. Operative Preparation and Flowmeter Equipment. The general arrangement of the animal and equipment are shown in figure 1. Twenty-five dogs weighing 7 to 22 Kg. (average 13.6) were anesthetized with 30 mg. per kilogram of sodium pentobarbital.* The femoral artery and vein of one hind leg, usually the left, were dissected free. The vein was prepared for peripheral cannulation while a small superficial arterial branch was prepared for central cannulation, the former to be used for venous outflow and the latter for the intra-arterial injections. Dissection was carried through from the femoral triangle to the sciatic sheath. Tourniquets were passed through and around the medial and lateral muscle masses and tightened so as to occlude all collateral venous and arterial channels,[5, 6] while excluding the femoral artery and vein and the femmoral and sciatic nerves. Cessation of venous outflow following occlusion of the femoral artery was used as evidence of effective occlusion of collateral circulation. In the opposite leg, the femoral artery was cannulated for registration of mean arterial pressure and the femoral vein for return of the blood obtained from the perfused leg. In many experiments, a pressure regulator[7] was connected to a cannula inserted into a carotid artery to assist in stabilizing the arterial pressure. Coagulation of the blood was prevented by heparin; the initial dose of 5 mg. per

* Kindly furnished by Premo Pharmaceutical Laboratories, New York, N. Y.

kilogram was followed by 1.6 mg. per kilogram every half hour thereafter.

The rate of outflow was measured by the piston-type of volume recorder shown in figure 2. This meter operates on the Gaddum[8] principle of a constant cycle length in which the height of each stroke indicates the rate of flow. The cycle length of 10 seconds used approximately two and a half seconds for filling and seven and a half seconds for draining. This timing allowed completion of both the filling and emptying phases during each 10 second cycle. The meter contained an L stopcock rotated by a solenoid which in turn was actuated from a relay connected with the laboratory timing circuit. When rotated to the *A* position the L stopcock connected the reservoir which collected blood from the femoral vein with the measuring tube in which was a piston recorder. When rotated to the *B* position the stopcock connected the measuring tube with a constant level outflow device which caused the piston recorder to return to the same point at the end of each stroke. With this device, there was never any outflow blood which was not measured. The recorder used had a range of 0 to 20 ml. per 10 seconds. This was quite adequate since, under control conditions, most of the hind legs studied had control flows of 2 to 6 ml. per cycle. Thus the meter had ample capacity to handle the increased flow seen during the experimental period. The over-all apparatus was calibrated by running fluid through it at various constant rates and measuring the amplitude of deflection. The calibration was linear. The apparatus is described more fully elsewhere.[9, pp. 71–73]

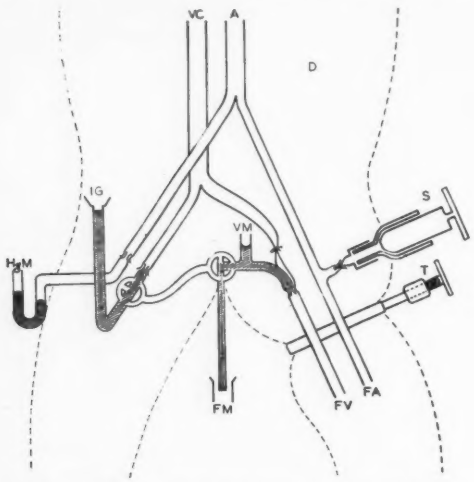


FIG. 1. Connections for measurement of flow in the isolated hind limb of the dog. *A*, aorta; *VC*, vena cava; *FA*, femoral artery; *FV*, femoral vein; *S*, tuberculin syringe for injection of drugs; *T*, tourniquet; *VM*, venous pressure manometer; *FM*, venous outflow meter; *IG*, blood reinfusion system; and *HgM*, mercury manometer for recording perfusion pressure. Shaded portion represents path of blood during flow measurement. When flow measurements are not being made, venous return can be directed from left into right femoral vein by rotating stopcocks.

The blood leaving the flowmeter was collected and reinfused into the dog every four minutes; the volume reinfused each time was approximately 100 ml. Blood for the initial filling of the pressure regulator and flowmeter and for providing a reserve of blood was obtained from a separate dog.

b. Control Experiments. In six control experiments methacholine, dissolved in pyrogen-free physiologic saline (0.2 μg. per ml.), was given in amounts of 0.2 to 0.8 ml. over a period of 20 seconds; control injections of the saline were given in like volume. In these control experiments flows and responses to the drug injections were recorded for one to two and three-quarters hours in the intact preparation; following this the vagi were severed and the carotid arteries ligated and flow responses recorded for two to six additional hours; the femoral and sciatic nerves were then cut as high as possible, and the flow responses were followed for an additional three and one-half hours. In experiment 2 the dog died at the time of nerve section; in experiment 3 the dog survived one-half hour and in experiment 4, one and one-quarter hours. In experiments 3 and 4 only one injection of methacholine was made after the nerve section. In experiments 5 and 6, flow responses were recorded for two and three and one-half hours in the intact preparation; after this the femoral and sciatic nerves were sectioned as high as possible and flow responses followed for three and three and one-half hours respectively. The total hours of perfusion were: experiment 1, nine and one-half hours; experiment 2, four and one-half hours; experiment 3, six and three-quarters hours; experiment 4, five and three-quarters hours; experiment 5, seven hours; and experiment 6, five hours.

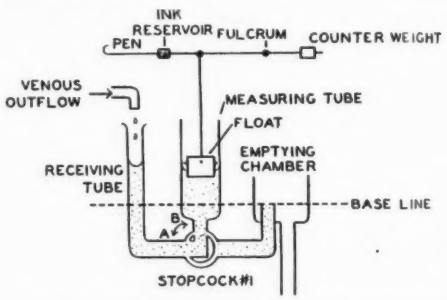


FIG. 2. Diagram of the flowmeter used in recording the venous outflow. See text for description.

c. Method of Preparation of Urines. All urine specimens were collected in autoclaved flasks from male subjects after careful cleansing of the penis and after discarding the initial voided urine. Part of the urine, indicated as *P*, was stored unaltered; another portion, *F*, was filtered through a Seitz filter; a third portion, *D*, was dialyzed in sterile viscose cellophane bags through frequent changes of distilled water at 4 to 9 C. for 24 hours; a fourth portion, *FD*, was both filtered and dialyzed. All samples were either used immediately, or were stored at −20 C. until used. Representative samples were found pyrogen-free using the rabbit as test animal. All equipment used in the preparation and storage of the urine was thoroughly washed and then rinsed with pyrogen-free saline before autoclaving. All specimens of urine were examined for clarity and frequent checks were made of the urine in various stages of preparation by inoculating the urine on tryptose phosphate broth and thioglycolate media. Cultures were read after 48 hours. Sterile, pyrogen-free saline, handled in the same manner as the urines, served as controls. Urines prepared in the above manner were studied for their vasomotor activity by intra-arterial injection into dogs as described above for methacholine. The potency of the urine was expressed in terms of the amount of methacholine required to give a similar vasodilator response.

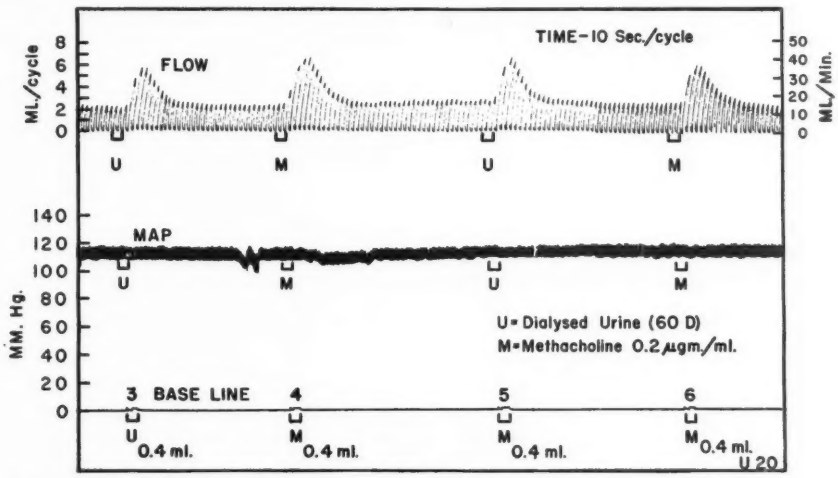


FIG. 3. Typical record of increases in flow produced by intra-arterial injection of a urine preparation and of 0.08 μg. of methacholine. See text for description.

RESULTS

A. *Method for Measuring Flow Curve*

Figure 3 shows a typical flow curve in which is recorded the response to two alternate intra-arterial injections of 0.4 ml. of urine and to two injections of 0.4 ml. of methacholine chloride (0.2 μg. per ml.) The flowmeter had a cycle length of 10 seconds (6 cycles per minute). The calibration on the left gives the flow per cycle. The calibration on the right gives the flow per minute represented by the amplitude per stroke of the flowmeter (that is, the flow per cycle × 60/cycle length in seconds). During the control period the flow was 2.4 ml. per cycle, that is, 14.4 ml. per minute. Within 2 to 3 cycles after the intra-arterial injection was started, the venous outflow had begun to increase. It reached maximums of 5.5 to 6.4 ml. per cycle (33 to 38 ml. per minute) in five cycles after the start of the injections and returned approximately to control values in seven cycles with the urine and in 10 cycles with the methacholine.

The responses to injections were analyzed as follows:

(1) ΔF (increment in flow) = MF (maximum flow) − CF (control flow).

(2) Per cent ΔF (percentile increment in flow) = $\frac{\Delta F \times 100}{CF}$.

Selection of the highest flow cycle during the response to the drug may lead to some variability, since the cycle length of the flowmeter

usually used was 10 seconds. However, this effect was minimized by making each of the injections at approximately the same moment in the flowmeter cycle. The method of calculation was checked also by integrating the flow throughout the vasodilator effect. This method did not give any more constant response than the use of the single greatest cycle. Since use of the highest cycle is much quicker and appeared to be equally as accurate we have expressed all the results in this paper in this manner. It was found by experience that a response equal to a 100 to 200 per cent increase in flow (per cent ΔF) was most convenient for use as the change was of sufficient magnitude to be measured easily, yet not so great that the effect lasted an excessive length of time.

B. Responses to Intra-arterial Injection of Saline

Control injections of the saline used in preparing the methacholine solution were given in volumes equivalent to those of the urine and reference solutions in most of the experiments. In most cases 0.4 ml. of the solution caused either no increase in flow, or a minimal, brief increment amounting to a percentile increment in flow (per cent ΔF) of 15 to 60. In one experiment saline caused percentile increments of flow of 90 to 147, comparable with those produced by the urine; this experiment was discarded.

C. Reference Vasotropic Substances

It was assumed that the response to a given amount of vasotropic substance would vary from animal to animal, but that the ratio of the response to substance *A* and the response to substance *B* might be somewhat more constant from animal to animal. If this were shown to be true then the potency of substance *B* could be expressed in terms of the amount of substance *B* required to give the same vasodilator effect as a standard amount of reference substance *A*. Two reference substances were examined, sodium nitrite and methacholine. It was found that 0.2 to 0.4 ml. of a 10 per cent solution of sodium nitrite gave percentile increases in flow ranging from 34 to 584 (average 138) in the nine experiments in which the substance was used; and, that 0.4 ml. of a solution containing 0.2 μg. per ml. of methacholine gave percentile increases in flow of 26 to 688 (average 162) in the 10 experiments in which it was used. The flow curves for sodium nitrite and urine were similar but sodium nitrite, upon repeated injection, tended to cause methemoglobinemia. Methacholine induced responses the duration and contour of which were similar to those caused by the vasodilator substances in urine. (See fig. 3.) Furthermore, the time interval between the drug administration and the beginning of response, the magnitude of response and the duration of response did not change markedly as the experiment progressed and no tachyphylaxis was noted to repeated injections of the methacholine.

D. Control Experiments using Methacholine

(*1*) *Magnitude of Control Flows.* As shown in table 1, the control flows ranged from 13 to 39 ml. per minute in the six intact preparations. The animal weights varied from 10 to 13 Kg. Since the perfused mass of the legs was not determined, no attempt was made to relate the flows to the mass of the extremity.

(*2*) *Variability of Control Flows in the Control Experiments.* In the six intact preparations (table 1) control flows decreased steadily in three dogs, falling 25 to 67 per cent; in one the flow rose 100 per cent; and in the remaining two control flows did not change significantly. The coefficient of variation for the control flows in these experiments ranged from 9 to 24 per cent (average 9 per cent). Mean arterial pressure in the various experiments ranged between 80 and 116 (average 101 mm. Hg); the coefficient of variation for mean arterial pressure in these six control experiments ranged between 1 and 11 per cent (average 6 per cent). Since, in five of the six experiments, mean arterial pressure fluctuated only ± 5 mm. Hg, the changes in control flow could not be correlated with the fluctuations in mean arterial pressure. Additional injections of anesthetic had to be given at irregular intervals. These injections (2 ml. of 3 per cent sodium pentobarbital) increased the control flow 30 per cent to 400 per cent and the increase in flow persisted for 5 to 10 minutes.

(*3*) *Effects of Vagal Section, Carotid Artery*

Ligation and Femoral and Sciatic Nerve Section on Control Flow in the Control Experiments. After a series of injections either the vagus nerves were sectioned and the carotid arteries ligated to minimize pressoreceptor influences, or the femoral and sciatic nerves were cut to eliminate nerve impulses going to the perfused leg. In one instance section of the vagus nerves and ligation of the carotid arteries caused the control flow to decrease almost immediately. In the three other experiments leg flow decreased after section of the vagus nerves and ligation of the carotid arteries, but the results were less clear cut because the control flow was declining at the time of the section. However, these procedures usually increased the variability of the perfusion pressures, the control flows, and maximum flows and the changes in flow. Following section of the femoral and sciatic nerves the control flows increased by 150 to 430 per cent in three of the four experiments in which prior section of the vagus nerves and ligation of the carotid arteries had been performed. The remaining dog of this group died at the time of nerve section. Section of the femoral nerves in the two intact animals caused 32 per cent and 100 per cent increases respectively in control flow.

(*4*) *Variation of Response to Repeated Injections of Methacholine in the Control Experiments.* In order to determine the reliability of the assay method, we made repeated injections of the same quantity of methacholine in each of the six control experiments. The results are shown in table 1, part I. Column A identifies the experiment; B gives the animal weight, C the number of similar injections, D the perfusion pressure (mean arterial pressure), E the control flow (*CF*), F the maximum flow (*MF*), G the maximum increment in flow (ΔF), and H the percentile increment in flow $\left(\frac{\Delta F}{CF} \times 100 = \text{per cent } \Delta F\right)$ in the intact preparations.

In the six intact animals (table 1), the maximum flows tended to vary slightly less than the control flows (coefficients of variation 4 to 16 per cent), but the increment in flow (ΔF) varied more than either the control flow or the maximal flow, that is, the coefficients of variability for ΔF were 4 to 41 per cent. When the results were expressed as per cent ΔF rather than as ΔF, the coefficients of variability were increased in three of the six experiments on the intact dogs, and were essentially unchanged in three (range 4 to 48 per cent).

(*5*) *Effect of Severing the Vagus Nerves, Ligation of the Carotid Arteries, and Section of the Femoral and Sciatic Nerves on the Variability of the Response to Methacholine.* The possibility was considered that changes in control flow due to variations in the activity of the reflex homeostatic mechanisms might be playing a part in causing the variability in response to successive injections. Therefore, as noted above, in several of the experiments (a) the vagi were severed and the carotid arteries ligated (column I, table 1); (b) the femoral and sciatic nerves were severed (experiments 5 and 6, column J, table 1), or (c) both procedures were carried out successively (experiment 1, column J, table 1). As shown in table 1, these procedures decreased the variability in two experiments and increased the variability of the changes in flow in two experiments.

(*6*) *Relationship of Response to Vasomotor Tone in the Extremity in the Control Experiments.* In attempting to determine some of the causes of variability of response to the methacholine, we analyzed the effects of changes of vasomotor tone upon the responses. Comparisons of pairs of injections, in the intact dogs, in which the perfusion pressure was constant but the control flow had varied, fairly consistently indicated that the response was greater the lower the control flow, that is, the higher the control vasomotor tone. During the increase of vasomotor tone that followed vagal and carotid section the responses tended to be decreased, and during the decrease in vasomotor tone that followed sciatic or femoral nerve section the responses tended to be increased. However, the change was not consistent enough to be taken as indicating a definite relationship. During the periods of increased flow which followed injections of additional amounts of anesthetic, the increments in flow in response to methacholine usually were less than those recorded just prior to the injection of anesthetic.

TABLE 1.—*Control Experiments. Variability of Responses to Repeated Injections of Methacholine and Urine*

			Intact Animal													After Vagi Cut and Carotid Arteries Ligated				After Cutting Femoral and Sciatic Nerves			
A	B	C	D		E		F			G			H			I	J			K	L		
Exp. No.	Wt. Kg.	No. of Injs.	Mean Art. Press. mm. Hg		CF Control Flow ml./min.		MF Maximum Flow ml./min.			ΔF ($MF - CF$) ml./min.			Percent ΔF $\left(\frac{\Delta F}{CF} \times 100\right)$			No. of Injs.	Per cent ΔF $\left(\frac{\Delta F}{CF} \times 100\right)$			No. of Injs.	Per cent ΔF $\left(\frac{\Delta F}{CF} \times 100\right)$		
			Range	Av.	Range	Av.	Range	Av.	C. of V.†	Range	Av.	C. of V.	Range	Av.	C. of V.		Range	Av.	C. of V.		Range	Av.	C. of V.
			I. Responses to Intra-Arterial Injections of Methacholine—0.4 ml. (0.2 μg./ml.)						%			%			%				%				%
1	12	7	112–124	116	14–20	17	42–53	46	8	26–35	29	18	130–202	168	18	8	27–235	105	67	10	87–233	168	25
2	12	9	100–118	109	13–25	19	38–46	42	7	15–29	22	19	66–218	130	40	9	57–150	112	28				
3	13	7	92–100	97	31–39	35	54–81	68	16	17–50	33	41	44–160	99	48	14	26–256	156	47				
4	13	3	84–86	85	24–30	27	44–49	47	6	17–25	20	21	62–103	76	31	9	123–256	220	19				
5	10	8*	110–116	112	10–18	15	37–41	39	4	20–28	25	12	110–287	182	36					8*	75–256	168	36
6	12	3*	80–98	87	31–36	33	91–102	94	7	60–66	62	4	184–198	192	4					3	29–71	51	41
Avs.....				101		24		56	8		32	19		141	29								
			II. Responses to Intra-Arterial Injections of Dialyzed Urine—0.4 ml. (60D)																				
5	10	8*	110–113	112	10–18	14	33–42	36	8	19–31	21	20	103–288	146	40					8*	117–410	189	50
6	12	3*	80–98	87	30–36	32	82–104	90	16	52–74	60	20	152–246	190	28					7	34–69	49	36
7	10	6	91–108	95	6–13	9	21–38	32	19	15–30	23	7	154–357	271	30					9	96–307	177	40

* Urine and methacholine injections given alternately.

† C. of V. equals standard deviation over mean × 100.

(7) *Variability after Omitting Data in Which Control Flows Varied Considerably from the Mean for the Group.* In view of the above noted effects of variations in control vasomotor tone, we selected from the data in table 1 only those observations in which mean arterial pressure and control flows were relatively constant, that is, in which vasomotor tone was relatively unchanged, and again computed the variability. This selection resulted in approximately a 30 per cent decrease in variability.

E. Vasodilator Effects of Urine and Various Urinary Extracts

(1) *Typical Flow Response to Urine.* Figure 3 reproduces two flow responses to the intra-arterial injection of 0.4 ml. of urine. As may be seen by comparison with the other two responses, the amplitude of the flow increment and the duration of the effect in this experiment is about the same as that noted with 0.08 μg. of methacholine.

(2) *Variability of Response to Repeated Injections of Urine into the Same Animal.* The effects of repeated injections of the same quantity (0.4 ml.) of the same dialyzed urine preparation (60D) were studied in three intact animals, (table 1, part II, columns A–H), and again in the same animals after cutting the femoral and sciatic nerves (columns K and L). Two of these animals (5 and 6) were the same as those used for testing methacholine; in these the injections of the urine preparation and methacholine were given alternately. There was no systematic variation in response which would suggest tachyphylaxis. The magnitude and the variability of the responses to the urine preparation were of the same order as those noted with methacholine. Section of the sciatic and femoral nerves increased slightly the variability of the response to the urine preparation in all three experiments.

(3) *Variation in Vasodilator Effect of the Urine in Different Experiments.* Plain sterile urine was injected intra-arterially in doses of 0.1 to 0.4 ml. in 16 intact animals. The percentile increment in flow (per cent ΔF) in the various experiments in response to 0.4 ml. of urine varied from 6 to 410 (average 180). When different urines were tested in the same animal they varied considerably in their potency. Urines from some human subjects possessed no vasodilator effects. Such urines were eliminated from the study. Injection of the same urine preparation into each of several legs gave responses which varied quite widely; the variation between leg preparations was, however, of the same order as that noted for methacholine.

(4) *Relationship of Vasodilator Effect of Urine to That of the Reference Substances.* Because of the wide variability of the response of both the reference substances and urine from test animal to test animal, we made repeated alternate injections of the same preparation of urine, and of methacholine in each of five dogs' legs. Table 2 shows the result of this comparison, using in each case 0.4 ml. of a dialyzed urine preparation (60D) and 0.4 ml. of the standard methacholine solution (0.2 μg. per ml.). The responses to both methacholine and urine varied considerably from time to time in each of the experiments. However the ratio of the response to methacholine to the response to urine remained relatively constant so long as pairs of injections, made near the same time in the experiment, were compared. Furthermore, as shown in table 2, despite the considerable fluctuation in the various responses from time to time in the same experiment, and from experiment to ex-

TABLE 2.—*Comparison of responses to 0.4 ml. of a dialyzed urine preparation (60D) and to 0.4 ml. of a solution of 0.2 μg. of methacholine per ml. All responses are expressed as percentile increment in flow (per cent ΔF).*

Intact Animals

Exp. No.	Urine Preparation			Methacholine			Ratio C/F
	A	B	C	D	E	F	
	Number of Injections	Range	Av.	Number of Injections	Range	Av.	
5	16	103–410	167	8	110–287	182	0.92
6	3	152–246	190	3	184–198	192	0.99
7	15	96–357	211	15	147–366	233	0.91
8	5	26–63	48	6	26–65	48	1.0
9	3	146–182	160	3	109–122	115	1.39
						Av.	1.06

In all experiments the injections of urine preparation and methacholine were given alternately.

periment, the ratios of the average response to the urine preparation, to the average response to the methacholine solution were relatively constant from experiment to experiment.

(*5*) *Relationship of Dose to Response.* In six experiments the responses were sufficiently stable so that an approximation of the dose-response relationship was attempted. Plots of the data from these six experiments were made on linear and on single and double logarithm paper. In general over the range of 0.2, 0.4, 0.8 and 1.6 ml. the closest approximations to straight lines were obtained on double logarithm paper. Figure 4 shows a plot for the data for a typical experiment. The slopes were such

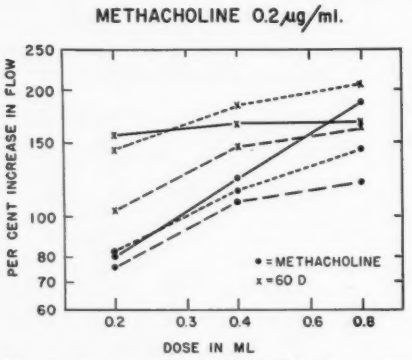


FIG. 4. Dose-response relationship for methacholine, plotted on log-log paper, with response expressed as percentile increase in flow.

that the percentile increments in flow were related to the dose according to the formula $R^x = K \cdot D$, where x varied between 1 and 3. The average value for x was 1.8.

(*6*) *Effect of Filtration and Dialysis on Vasodilator Activity of Urine.* Urines, prepared as described under Methods, were injected into test preparations. The vasodilator responses of the treated preparations were related to that on the original untreated urine. In seven experiments six different urines were tested. The average of the results of 15 sets of injections of each of the four kinds of urine preparations were as follows: filtered urine possessed 80 per cent, dialyzed urine 80 per cent, and filtered and dialyzed urine 70 per cent, of the vasodilator activity of the untreated urine. In all but one of the 15 trials, the vasodilator effect of the plain urine was as great as or greater than that of the treated urines. When pairs of responses to filtered and dialyzed urine were compared the latter was on the average 23 per cent less effective. However this average difference was not statistically significant and in four of the 15 pairs of injections the dialyzed urine gave a greater response than the filtered urine.

DISCUSSION

Using the Dumke and Schmidt bubble flowmeter as a measure of control femoral artery blood flow, Kemp, Paul and Hines[11] found average flows of 40 ml. per minute and 74 ml. per minute for two dogs. Higher average flows of 120 ml. per minute and 106 ml. per minute for two different dogs were later described. The lower flows previously recorded by these authors were thought by them to be the result of experimental error in that they had not waited a sufficient time for stabilization. Siems, Kosman and Osborne,[12] using a modified Leden bubble flowmeter, noted average control flows of 42 ml. per minute. Richardson and co-workers,[13] using the electromagnetic flowmeter, found control flow values of 59 to 66 ml. per minute. In our series the average control flows ranged from 9 ml. per minute to 35 ml. per minute or approximately one-half of that found by other investigators. Our lower flows may have been due: (1) to the use of smaller animals (the dogs in our control experiments weighed 10 to 13 Kg.); (2) to perfusion of a smaller fraction of the leg mass, or (3) to development of a shocklike state with vasoconstriction as a result of trauma incident to the preparation of the leg for flow measurement.

We have been unable to find any literature primarily devoted to study of blood flow responses to methacholine with which to compare our results. An injection of 0.4 ml. of methacholine solution (0.08 µg.) produced a wide range of change of flow in the intact control experiments (+44 per cent to +287 per cent). The variation in response was considerably less within a single animal, but still such as to give coefficients of variation of 4 to 48 per cent.

The possible causes of the variability in flow following drug injections are numerous. They include changing vasomotor tone in the per-

fused leg due to spontaneous alterations in the activity of the vasomotor center and to the occasional injections of additional anesthetic, fluctuations in viscosity, alterations in mean arterial pressure, variations in the rate of drug injection, and development of refractoriness to the drug. No obvious refractoriness to either the methacholine or the urine preparations was noted. The rate and time of the drug injections was kept as constant as possible. Elimination of the effects of variations in activity of the pressor receptor organs and of the direct influence of the vasomotor center upon the leg by section of the femoral and sciatic nerves did not significantly reduce the variability of response to methacholine. The variability was considerably reduced by selection of experiments in which vasomotor tone was fairly constant. This suggests that part of the variability was due to irregular fluctuations in the concentration of circulating vasotropic substances.

The range of variation of the responses to methacholine was fairly large with the assay method described in this paper, but it was less than that obtained by recording the effects of vasodilator drugs on mean arterial pressure. Furthermore, when the vasodilator effect of urine was related to that of methacholine in pairs of injections given closely together in the same experiment, the measure of relative potency of the urine was much more constant. Since the method also demonstrates the precise peripheral vasodilator effects of the drug, we believe this procedure possesses advantages over registration of mean arterial pressure in the study of vasotropic substances.

A previous report[3] has shown the presence of a depressor substance in human urine which may be the same as that described by Wollheim,[14, 15] but probably different from that described by Westerfeld and co-workers.[16] The vasotropic principle causes an increase in cardiac output and a decrease in mean arterial pressure.[4] This paper demonstrates that urine and urine extracts possess a direct peripheral vasodilator action. This vasodilator effect is probably responsible, at least in part, for the depressor effect of urine.

The vasodilator effect is not due to the presence of pyrogenic substances since it is obtained with preparations of urine which are demonstrated to have been sterile throughout their process of handling and, furthermore, such preparations do not induce pyrogenic reactions when injected into rabbits. Pyrogen-free saline, handled in the same way as the urine, also does not develop significant vasodilator properties.

A vasodilator effect equivalent to that induced by 0.08 μg. of methacholine injected intra-arterially is produced by 0.4 ml. of plain urine obtained from many but not all subjects. The dose of urine or methacholine usually has to be increased roughly as the square (average 1.8 power) of the response, when the response is expressed as the percentile increase in maximum flow per cycle of the flowmeter. The vasodilator substance is reduced in potency by only 20 to 30 per cent by filtration and dialysis. This loss may be due to adsorption.

Summary

We have studied the blood flow response to methacholine injected intra-arterially in an isolated, blood-perfused leg. In a series of six control experiments, graphic and statistical studies were made of control flows, and of the changes in flow produced in the intact and in the denervated isolated leg by intra-arterial injections of methacholine. The responses to repeated injections of the drug varied considerably (coefficients of variation were 18 to 48 per cent). No tachyphylaxis to methacholine was demonstrated.

Section of the vagus nerves and ligation of the carotid arteries consistently reduced the control flows; section of the sciatic and femoral nerves and injections of the anesthetic regularly increased control flow, particularly if performed when vasomotor tone was high as a result of the preceding procedures. Neither removal of the active reflex homeostatic mechanisms (section of the vagi and ligation of the carotid arteries) nor section of the sciatic and femoral nerve supplying the perfused leg decreased the variability of the flow responses to methacholine. Elimination of data in which control flow varied considerably from the mean of the group resulted in a significant decrease in the variability of the responses to methacholine.

A vasodilator substance is present in normal

human urine which cannot be attributed to bacterial contamination. The substance is only partially removed by Seitz filtration and dialysis through cellophane bags in distilled water. Its action appears to be peripheral, since it produces its effect when given directly intra-arterially in the intact or denervated extremity. No tachyphylaxis is noted to repeated injections. The concentration of this substance varies considerably in different urine specimens. On the average the amount present in 0.4 ml. of urine is approximately equivalent in vasodilator effect to that of 0.08 μg. of methacholine.

Despite the variability of the responses to methacholine and to urine, the ratio of the response to urine and the response to methacholine in closely adjacent pairs of injections remained quite constant. This method appears to offer certain advantages over registration of the effects of vasotropic substances on mean arterial pressure in the bioassay of vasotropic substances, particularly when their potency is related to that of a standard vasotropic substance.

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The Effect of Sympathectomy for Essential Hypertension on the Hallucal Circulation

By Milton Mendlowitz, M.D., and Arthur S. W. Touroff, M.D.

The effects of sympathectomy on the hallucal circulation were studied in patients with essential hypertension. Return of sympathetic nerve function of variable degree could be demonstrated in every patient. An increase in non-neurogenic or intrinsic resistance was also found to be attributable to the sympathectomy. This could not be reversed by benzodioxane and was therefore probably not produced by circulating epinephrine. The possible mechanisms of this phenomenon are discussed.

IT IS generally agreed that sympathectomy produces an increase in blood flow in a normal extremity. This is manifested by an increase in skin temperature when comparison is made with the contralateral extremity not subjected to sympathectomy.[1] It also has been demonstrated in animals that, to a variable extent, sympathetic nerve tone returns after sympathectomy.[2] In addition, the maximal blood flow obtainable after release of residual sympathetic nerve tone often declines gradually to a point somewhere between previous maximal and extreme vasoconstrictive levels.[1] Thus when the body is warm, blood flow may be less on the sympathectomized than on the normal side, whereas the opposite may be true when the body is cool. This decline in maximal blood flow after sympathectomy has been attributed to the effect of circulating epinephrine and it can be demonstrated by epinephrine perfusion experiments that denervated blood vessels react to epinephrine by constricting.[3] There is controversy, however, as to whether these reactions are greater than normal.[3, 4] There is, in addition, no conclusive evidence that sufficient epinephrine is in the circulation to account for the postsympathectomy decrease in maximal blood flow as it is usually measured.

To clarify these points, 21 patients who had been subjected to operation for hypertension were studied. Standard thoracolumbar sympathectomies had been carried out in these patients from two to five years prior to these studies. Brachial blood pressure and blood flow in the great toe were measured with the patient at rest in a quiet room. These determinations were repeated after the application of indirect heat with a cradle-baker over the trunk for 30 to 60 minutes, supplemented by the intravenous administration of 5 mg. per kilogram of tetraethylammonium chloride. The measurements were repeated again after the intravenous injection of 10 mg. of benzodioxane per square meter of body surface. Brachial blood pressure was measured by the standard method with a mercury manometer and cuff, whereas blood flow in the great toe was measured calorimetrically.[5] The drugs were injected slowly via the tubing of an intravenous apparatus containing physiologic salt solution.

The results are presented in table 1. Dimensional changes in the digital vessels were estimated crudely from changes in the vascular volume index.[6] This is the flow–mean pressure ratio multiplied by a constant and is the reciprocal of resistance in dyne seconds per cm^5. These determinations cannot be made more precisely because digital blood pressure measurement, especially of the diastolic phase, is inaccurate in the toe. Directional changes in blood pressure, however, are determined largely by changes in the systemic resistance as a whole rather than by local changes in any vascular bed, and the error introduced by the use of brachial arterial blood pressure is probably small. Atmospheric conditions were kept as uniform as possible in a quiet room in which

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TABLE 1.—*Hallucal Circulation in Essential Hypertension after Sympathectomy*

Name	Age and Sex	Diagnosis	Pre-op. B.P.	Date of Operation	Operation	Date of Test	Pre-TEAC and Indirect Heating			Post-TEAC and Indirect Heating			Post-Benzodioxane		
							Digital B. Flow *cc./cm.²/min.*	Brachial B. P. *mm.Hg.*	Vasc. Vol. Index μ^3	Digital B. Flow *cc./cm.²/min.*	Brachial B. P. *mm.Hg.*	Vasc. Vol. Index μ^3	Digital B. Flow *cc./cm.²/min.*	Brachial B. P. *mm.Hg*	Vasc. Vol. Index μ^3
E. R.	34 F	Ess. hyper.	234/107	6-47	Rt. sympathec. D5-L2. Complete splanchnicec.	5-50	0.01 Rt.toe	216/132	10	0.19 Rt.toe	170/120	256	0.20 Rt.toe	194/140	233
			180/136	4-49	Lt. sympathec. D6-L3. Complete splanchnicec.										
H. S.	54 F	Ess. hyper.	280/156	4-48	Rt. sympathec. D5-L2. Greater and lesser splanch.	9-50	0.10 Lt.toe	266/134	97	0.19 Lt.toe	170/105	270	0.20 Lt.toe	240/130	210
			270/150	7-48	Lt. sympathec. D4-L2. Greater and lesser splanch.										
J. P.	53 F	Ess. hyper.	216/130	8-47	Rt. sympathec. D4-L3. Greater splanchnicec.	9-50	0.13 Lt.toe	182/100	181	0.21 Lt.toe	156/110	310	0.20 Lt.toe	195/130	239
			188/112	9-47	Lt. sympathec. D4-L3. Greater splanchnicec.										
R. R.	50 F	Ess. hyper.	230/110	5-47	Rt. sympathec. D4-L3. Geater splanchnicec.	9-50	0.20 Lt.toe	210/110	244	0.21 Lt.toe	160/90	331	0.21 Lt.toe	202/104	268
				6-47	Lt. sympathec. D4-L3. Greater splanchnicec.										
O. P.	38 M	Ess. hyper.	185/130	4-46	Lt. sympathec. D4-L2. Greater splanchnicec. Adrenal denervation	11-50	0.11 Lt.toe	148/98	176	0.13 Lt.toe	145/95	214	0.14 Lt.toe	150/95	224
			180/140	6-46	Rt. sympathec. D4-L2. Greater splanchnicec. Adrenal denervation										
R. S.	51 F	Ess. hyper.	210/120	10-46	Rt. sympathec. D4-L2. Greater splanchniec. Partial celiac ganglionec. Adrenal denervation.	11-50	0.21 Lt. toe	166/86	328	0.24 Lt. toe	120/82	474	0.22 Lt. toe	160/95	338
			210/120	11-46	Lt. sympathec. D4-L2. Greater splanchnicec. Partial celiac ganglionec. Adrenal denervation.										
S. K.	52 M	Ess. hyper.	240/100	1-46	Rt. sympathec. D4-L2. Greater splanchnicec. Partial celiac ganglionec. Adrenal denervation.	1-51	0.06 Lt. toe	174/90	89	0.11 Lt. toe	190/100	148	0.11 Lt. toe	185/100	151
			236/144	2-46	Lt. sympathec. D4-L2. Greater splanchnicec. Partial celiac ganglionec.										
M. B.	55 M	Ess. hypert.	260/150	3-48	Lt. sympathec. D5-L3. Complete splanchnicec.	8-50									
				4-48	Rt. sympathec. D5-L3. Complete splanchnicec.		0.08 Lt. toe	208/126	93	0.08 Lt. toe	162/112	115	0.09 Lt. toe	225/120	101
J. P.	38 M	Ess. hyper.	205/135	5-48	Rt. sympathec. D3-L2. Greater splanchnicec.	8-50									
			184/120	5-48	Lt. sympathec. D4-L2. Complete splanchnicec.		0.05 Lt. toe	148/106	78	0.09 Lt. toe	140/110	142	0.12 Lt. toe	160/100	182
A. G.	36 M	Ess. hyper.	152/110	3-48	Rt. sympathec. D2-L3. Complete splanchnicec.	8-50	0.18 Lt. toe	138/106	291	0.20 Lt. toe	120/82	395	0.19 Lt. toe	130/110	313
					Lt. sympathec. D2-L2. Greater splanchnicec.										
E. S.	45 M	Ess. hyper.	250/172	1-48	Rt. sympathec. D6-L1	8-50	0.09	162/134	119	0.11	164/130	146	0.09	168/125	120
S. T.	47 F	Ess. hyper.	250/120	7-46	Bilateral sympathec. D4-L2. Complete splanchnicec. Adrenal denervation	12-50	0.21 Rt. toe	196/98	279	0.23 Rt. toe	160/94	357	0.22 Rt. toe	180/108	299

					Lt. sympathec. D2-L2. Greater splanchnicec.										
E. S.	45 M	Ess. hyper.	250/172	1–48	Rt. sympathec. D6-L1.	8–50	0.09	162/134	119	0.11	164/130	146	0.09	168/125	120
S. T.	47 F	Ess. hyper.	250/120	7–46	Bilateral sympathec. D4-L2. Complete splanchnicec. Adrenal denervation	12–50	0.21 Rt. toe	196/98	279	0.23 Rt. toe	160/94	357	0.22 Rt. toe	180/108	299
M. N.	47 M	Ess. hyper.	210/110	6–46	Bilateral sympathec. D4-L2. Celiac ganglionec. Greater splanchnicec. Adrenal denervation	12–50	0.06 Lt. toe	228/138	64	0.17 Lt. toe	230/130	183	0.16 Lt. toe	208/136	181
J. M.	52 M	Ess. hyper.	190/?	6–47	Rt. sympathectomy D4-L2 Right adrenal denervation	8–50	0.06 Rt. toe	142/96	100	0.05 Rt. toe	110/70	112	0.05 Rt. toe	144/88	85
			120/92	2–48	Lt. sympathec. D4-L2; Lt. adrenal denervation.										
M. D.	26 F	Ess. hyper.	220/140	6–48	Sympathec., rt. D5-L3. Greater splanchnicec.	4–50									
			240/160	9–48	Sympathectomy, lt. D5-L3. Greater splanchnicec.		0.09 Rt. toe	244/184	81	0.13 Rt. toe	194/160	143	0.13 Rt. toe	218/180	126
R. S.	34 F	Ess. hyper.	236/162	12–49	Lt. sympathec. D8-L2 Complete splanchnicec.	5–50	0.21 Rt. toe	176/126	272	0.18 Rt. toe	138/108	289	0.17 Rt. toe	136/104	280
				12–49	Rt. sympathec. D9-L3 Complete splanchnicec.										
F. R.	38 F	Ess. hyper.	215/138	1–45	Rt. sympathec. D4-L2; Partial celiac ganglionec. Adrenal denervation	3–51	0.04 Lt. toe	188/126	50	0.09 Lt. toe	140/115	138	0.10 Lt. toe	180/130	126
			160/105	9–45	Lt. sympathec. D4-L2; Complete splanchnicec. Partial celiac ganglionec. Adrenal denervation.										
R. H.	29 F	Ess. hyper.	160/100	7–45	Rt. sympathec. D4-L2. Complete splanchnicec. Partial celiac ganglionec. Adrenal denervation.	4–51	0.09 Lt. toe	148/98	144	0.26 Lt. toe	126/95	464	0.27 Lt. toe	120/95	497
			170/104	8–45	Lt. sympathec. D4-L2. Complete splanchnicec. Partial celiac ganglionec. Adrenal denervation.										
A. C.	52 F	Ess. hyper.	218/134	7–46	Lt. sympathec. D4-L2. Complete splanchnicec. Partial celiac ganglionec. Adrenal denervation.	2–51	0.12 Lt. toe	222/130	132	0.13 Lt. toe	172/112	179	0.14	254/154	133
			184/120	9–46	Rt. sympathec. D4-L2. Complete splanchnicec. Partial celiac ganglionec. Adrenal denervation.										
D. R.	41 F	Ess. hyper.	184/104	10–46	Rt. sympathec. D4-L2. Complete splanchnicec. Partial celiac ganglionec. Adrenal denervation.	3–51	0.18 Lt. toe	212/126	207	0.17 Lt. toe	174/114	231	0.17 Lt. toe	210/120	201
			168/92	11–46	Lt. sympathec. D4-L2. Complete splanchnicec. Partial celiac ganglionec. Adrenal denervation.										
I. S.	37 M	Ess. hyper.	270/130	4–45	Rt. sympathec. D4-L2. Complete splanchnicec. Partial celiac ganglionec. Adrenal denervation.	1–51	0.12 Lt. toe	162/114	171	0.14 Lt. toe	132/100	239	0.14 Lt. toe	155/110	207
			190/130	6–45	Lt. sympathec. D4-L2. Complete splanchnicec. Partial celiac ganglionec. Adrenal denervation.										

automatic controls of temperature and humidity were not available. In the resting state, the emotions of the individual tended to cause neurogenic vasoconstriction, the other factor that acted oppositely, being the degree of "success" of the sympathectomy. Despite these complexities, the figures clearly demonstrate residual sympathetic nerve tone of varying degree in every patient (fig. 1).

It should also be noted that sympathectomized patients with hypertension had blood flow readings, after release of sympathetic nerve

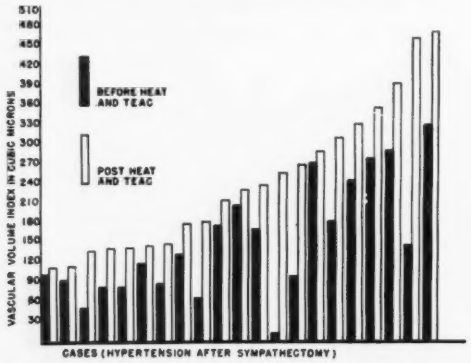


FIG. 1. Vascular volume index (flow-pressure ratio) before and after release of residual sympathetic nerve tone by indirect heating and tetraethylammonium chloride (5 mg. per kilogram). *Black bars:* Mean 153. Standard deviation 86. Standard error of the mean 19. *White bars:* Mean 245. Standard deviation 107. Standard error of the mean 24. Standard error of the difference of the means 31. Significance ratio 3.0.

tone, which were lower than similar flow readings in a comparable group of patients with established uncomplicated hypertension (fig. 2). This would indicate that the operation produced an increase in non-neurogenic, or intrinsic, resistance in the toe. The general effect of this would be to increase the blood pressure "floor" after heat and tetraethylammonium chloride[7] moderately, so that any change in "floor" blood pressure would be upwards. Advance of underlying renal and vascular disease would also tend to raise rather than lower "floor" blood pressure. Unless there were an extreme decrease in the blood pressure "floor," which thus is unlikely, the decreased blood flow in the toe after release of sympathetic nerve tone must represent a sharp increase in intrinsic resistance caused by the sympathectomy. Such changes have been described after sympathectomy for a variety of diseases including hyperhidrosis,[8] and are confirmed in these observations.

The results are unequivocal (fig. 3) in indicating no decrease in intrinsic resistance after the administration of benzodioxane. Resistance was either unchanged, slightly increased, or slightly

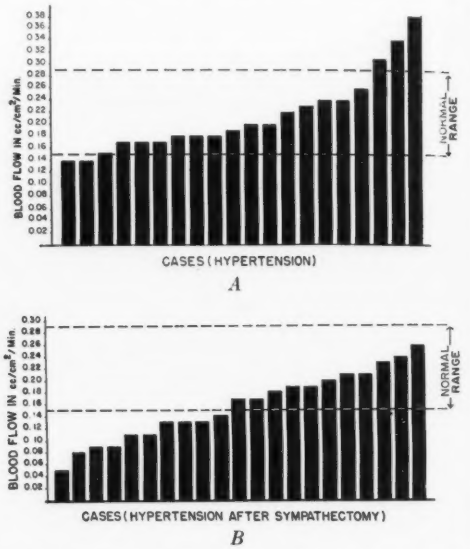


FIG. 2. Blood flow after release of sympathetic nerve tone by indirect heating and tetraethylammonium chloride (5 mg. per kilogram).

A. Mean 0.214. Standard deviation 0.066. Standard error of the mean 0.015. *B*. Mean 0.158. Standard deviation 0.055. Standard error of the mean 0.012. Standard error of the difference of the means 0.019. Significance ratio 2.9.

decreased, even in those patients with a demonstrable increase in intrinsic resistance after operation. In several cases, the increase in resistance produced by benzodioxane was associated with an alarming increase in heart rate, an effect already described.[9]

In figure 4, the extent of the return of sympathetic nerve function, as manifested by the difference in vascular volume indexes before and after release of residual sympathetic nerve tone, are plotted against the degree of increase in intrinsic resistance produced by the sym-

pathectomy as measured by the level of blood flow after release of sympathetic nerve tone. The correlation is marred by the variable factor of emotion in the "resting" state but still is suggestive of a trend toward greater increase in intrinsic or non-neurogenic resistance in these cases with the least residual sympathetic nerve tone. The more "successful" the operation, then, the greater the apparent tendency to counteract neurogenic vasodilatation by the development of intrinsic, or non-neurogenic vasoconstriction. There is no significant correlation between the difference in blood pressure before and after release of residual sympathetic nerve tone and the intrinsic resistance as measured by the blood flow level after indirect heating and tetraethylammonium chloride. This tends to exclude incomplete release of sympathetic nerve tone as an important factor. It is also unlikely that sympathetic nerve tone was more completely released in the hypertensive group than in the patients subjected to sympathectomy.

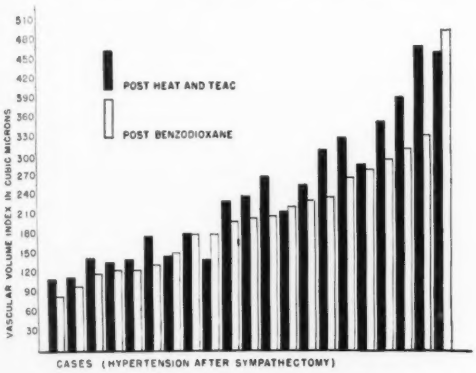


FIG. 3. Vascular volume index (flow-pressure ratio) after release of residual sympathetic nerve tone by indirect heating and tetraethylammonium chloride (5 mg. per kilogram) compared with index after benzodioxane (10 mg. per square meter of body surface). *Black bars:* Mean 245. Standard deviation 107. Standard error of the mean 24. *White bars:* Mean 215. Standard deviation 94. Standard error of mean 21. Standard error of difference of means 32. Significance ratio 0.9.

DISCUSSION

It is clear that sympathectomy as ordinarily performed for hypertension does not totally interrupt sympathetic nerve outflow to the lower extremities permanently. This may be due in part to some bridging of the nerve gaps, but also may be caused by the assumption of function of small nests of sympathetic ganglion cells in the anterior spinal nerve roots, the pre- and postganglionic fibers of which are not interrupted by the operation.[2] What is more, the degree of sympathetic nerve tone which returns is probably variable, if one can safely disregard the factors of atmospheric variation and emotion.

It is also clear that sympathectomy in some manner often produces an increase in non-neurogenic or intrinsic vascular resistance. If the failure of these vessels to dilate after the administration of benzodioxane signifies the absence of sufficient circulating epinephrine to account for this intrinsic vascular narrowing, whether or not the denervated vessels are more sensitive to such stimulation, some other explanation must be sought for the phenomenon.

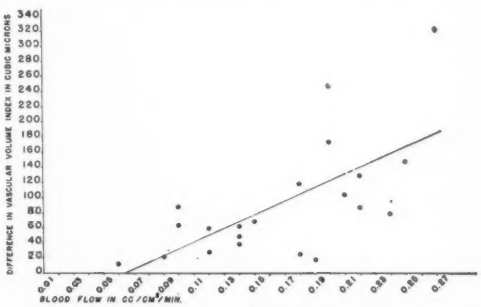


FIG. 4. Difference in vascular volume index before and after release of sympathetic nerve tone correlated with blood flow after release of sympathetic nerve tone. Correlation index is 0.7.

The possibilities are (a) sensitization of the denervated vessels to some circulating substance other than epinephrine, (b) changes produced by the operation in such components of tissue metabolism as hydration, salt content, or oxidation with a corresponding influence on vascular caliber and reactivity and (c) the development because of decreased nervous stimulation of atrophy of disuse and hence shortening of the circular arteriolar smooth muscle. Although (a) and (b) are not completely excluded, the fact that the increased

intrinsic resistance develops gradually[1] and seems to be greater in those patients with less residual sympathetic nerve tone favors the third hypothesis, namely, that the greater the "success" of the sympathectomy the greater the increase in intrinsic resistance because of disuse atrophy and shortening of the circular smooth muscle of arterioles.

Summary and Conclusions

The hallucal circulation of patients subjected to sympathectomy for hypertension was studied. Sympathetic nerve tone always returned to a variable extent after operation. The sympathectomy, in addition, often produced an increase in intrinsic non-neurogenic vascular resistance. This increase in resistance could not be reversed by benzodioxane and hence was probably not attributable to the effect of circulating epinephrine. Since there was a tendency for greater increase in intrinsic vascular resistance when there was less return of sympathetic nerve function, such increase might have been caused by relative disuse atrophy and shortening of the circular smooth muscle of arterioles.

Acknowledgment

The advice of Dr. S. Feitelberg and the technical assistance of Mr. Ralph E. Schwartz are gratefully acknowledged.

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The Factors Influencing the Circulation Time

By MORTON LEE PEARCE, M.D., ALVIN E. LEWIS, M.D., AND MELVIN R. KAPLAN, M.D.

A mathematical analysis of the relationship of cardiac output and heart-lung blood volume to observed circulation time is presented. The theoretic conclusions are substantiated by an experiment in which it is shown that diluting the amount of indicator used prolongs the observed circulation time through the heart and lungs.

THE MEASUREMENT of the circulation time through the heart and lungs is one of the most widely used tests of circulatory efficiency in clinical medicine. Yet, surprisingly, the term is usually poorly defined, and there is certainly considerable disagreement concerning its parameters. As Wiggers[1] points out, circulation time is *not* the time required for the blood to make a complete circulation, because any given corpuscle has such a wide variety of paths over which to travel as to make such a concept meaningless. With many authors the term "circulation time" seems to imply a measure of the mean velocity of flow of an injected substance from the point of injection to the place of detection. Blumgart[2] in his informative review remarks that velocity of blood flow as such cannot be measured and defines the measurable circulation time as being "the interval of time necessary for the fastest particle of a foreign substance to traverse the shortest available path between the point of injection and the place of detection."

If a given amount of indicator is injected at time T_0, and the concentration of indicator at the place of detection is plotted against time, then, disregarding recirculation, a curve, as shown in figure 1, will be obtained. This has been demonstrated by Hamilton and co-workers[3a, b] in their studies on an injection method for the determination of cardiac output. Following Blumgart's definition, the circulation time would be the time interval from the instant of injection (T_0) to the instant (T_1) when the first particle of indicator appears. If the time interval measured were the time of mean appearance of the injection mass then the circulation time on this ideal curve would be from T_0 to that point on the curve (T_3) when half of the area under the curve was between these two points. However, it would seem that, whether the end point be detected objectively (fluorescein) or subjectively (Decholin), the circulation time is determined neither by the appearance of the first particle of indicator nor by the appearance of half the indicator. Rather it would seem that the circulation time actually observed is the time required for an injected indicator to reach a detectable concentration at the place of detection. If this threshold or minimum detectable concentration be assigned the value (P'), then the observed circulation time is the time interval between the injection (T_0) and the time (T_2) when the concentration (P') is reached. It follows that any discussion of the factors controlling the circulation time must be consistent with this definition.

As mentioned, various parameters have been assigned to circulation time. Wiggers[1] states that the test gives "only rough information regarding changes in the circulation; indeed, an analysis of where and why changes occurred can generally not be made." However, it is almost universally recognized that as a clinical test the circulation time is useful in both establishing diagnoses and following the course of disease. It becomes prolonged in congestive heart failure and returns toward normal with relief of failure, although it is usually normal or rapid in heart failure due to anemia, thyrotoxicosis, beriberi and arteriovenous fistula. Blumgart[2] demonstrated that the circulation time is affected by the cross-sectional area of the pathway traveled, which in turn is a function of the amount of blood in the pulmonary

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vascular bed and the condition of its vessels. Other things being constant, it can be seen that a widening of the pathway will allow the same volume per unit time to pass at a diminished speed. However, if narrowing of the vascular caliber significantly impedes flow, slowing will occur. Again Blumgart assigns great importance to the relationship of cardiac output and velocity of flow. Increasing minute output increases the rate of flow (and decreases circulation time) if other factors remain the same.

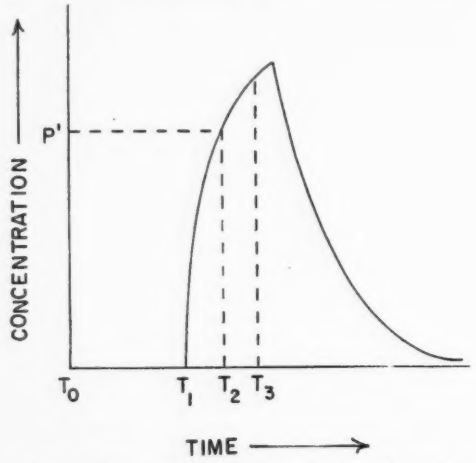


FIG. 1. Diagrammatic representation of concentration of indicator plotted against time. Recirculation is disregarded. P', threshold level; T_0, onset of injection; T_1, time of arrival of indicator; T_2, time of taste onset; T_3, mean appearance time of injected mass.

Decreasing cardiac output has the opposite effect. Thus in myxedema without heart failure the circulation time is prolonged[2,4] in association with a diminished cardiac output. Conversely, circulation time is notoriously rapid in Grave's disease, even with heart failure and dilatation of the vascular bed, both of which would tend to prolong it. This must be due to the marked increase in cardiac output which commonly occurs in hyperthyroidism. In the usual case of congestive heart failure circulation time is prolonged even more than it would be in a case of myxedema with the same reduction in cardiac output, because pulmonary engorgement adds its slowing effect.

Recently Nylin,[5,6] following David and Bouvrain,[7] has emphasized the effect of cardiac dilation on circulation time. He suggests that a dilated, poorly emptying heart will prolong circulation time by a diluting effect, and has published studies in which he has correlated circulation time with heart volume as measured by his x-ray technic. Meneely and Chesnut[8] have made a similar study and have found a high degree of correlation between the ratio (transverse diameter of the heart/intrathoracic diameter)[3] and circulation time. They admit that Nylin's observations in patients with congestive failure of a prolongation of the taste sensation and a flattening of the red cell dilution curve are correct, but they state that this effect could not substantially delay the arrival of the first portion of the injected indicator. They include in their criticism, as does Altschule,[9] the objection that a high degree of correlation does not in itself show a causal relationship and that both cardiac dilation and prolonged circulation time may be dependent on other factors such as diminished cardiac output.

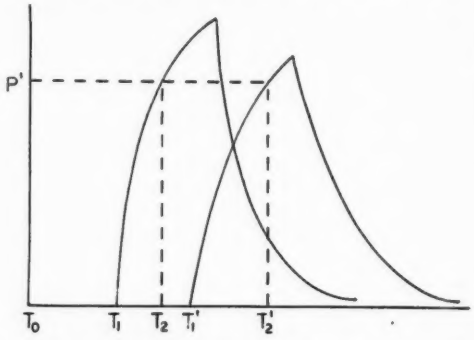


FIG. 2. Effect of congestive failure on components of circulation time. T_1' and T_2' are prolonged. Recirculation is disregarded.

Although this *post hoc* relationship does not in itself prove a causal connection it would seem that a case can be made for Nylin's thesis. The end point of the circulation time is determined not by the arrival of the first particle but by the arrival of a detectable concentration of indicator at the place of detection. As a consequence of this threshold effect and the fact that the indicator cannot be injected instantaneously, the greater the dilution of the

injected substance the longer it will take for the threshold concentration to be reached. In other words, the greater the volume of blood between the points of injection and detection, the more gradual will be the ascent and descent of the rising and falling-off curves of concentration plotted against time and the longer it will take for the threshold concentration (P') to be reached (fig. 2). This effect, rather than laminar flow, probably accounts for the "stringing out" phenomenon which has been discussed in the literature.[2] Both the rising and falling-off curves are, to the extent which they are determined by this factor, exponential.

This conclusion is justified by data already in the literature. Nylin's[6, 10] red corpuscle dilution curves show a more gradual ascent and falling off in patients with congestive failure. Also, it is a well recognized clinical observation that, in patients with congestive failure, the end point of a circulation time determination tends to be diffuse rather than sharp, and the effect builds up gradually and may last longer. Further, Hitzig[11] in his work on ether arm to lung circulation times found that if he made the ether dose small enough there was not only a poorly defined, but also a prolonged end point in normals. The effect of dose on time-concentration is shown schematically in figure 3 when P' is again the minimal detectable concentration.

Other factors affecting circulation time can be discarded or defined in terms of one of the above factors. Blumgart[2] assumes that the path traveled is relatively uniform from patient to patient as is shown by the relatively small range of normal circulation times. And certainly laminar flow must be minimal in a system with pulsations, changing frictions, changing diameters, turns and branchings. The viscosity of the blood will be reflected in the cardiac output, dilution and cross-sectional parameters. For example, in anemia the cardiac output increases and the blood volume decreases with a resulting rapid circulation time. Conversely, in polycythemia the cardiac output is normal,[12] but the plethora causes an increase in cross section of the blood channels and a greater dilution of indicator and so the circulation time may be prolonged.[2, 12] Diminution of the available cross-sectional area will, after a certain point is reached, impede flow. Other things being equal this effect will be mirrored by a diminution in cardiac output. An additional factor suggesting itself is the relation of the time of injection to the phase of the cardiac and respiratory cycles. Even in a case of complete heart block it is difficult to imagine the phase of the cardiac cycle having an effect of more than a second or so, and moderate increases in respiration are known to have little effect on cardiac output.[13] Breath holding diminishes blood flow in the lungs and should be avoided in performing the test.

Therefore, it would seem that the circulation time, as here defined, is a function of (1) the cross-sectional area of the pulmonary vascular bed (controlled by the volume of blood in the lungs), (2) the cardiac output (itself affected by factors such as peripheral resistance), and (3) the amount of dilution of the injected mass by the blood in the heart and lungs. It can be seen that the blood volume factor affects the observed circulation time in two ways: (1) the simple linear velocity effect controlled by cross-section, and (2) the exponential delay in reaching a perceptible concentration produced by the diluting pool of blood in the heart and lungs. Referring to figure 1, the linear effect results in the time from T_0 to T_1 while the exponential or "pool" effect results in the time from T_1 to T_2 where a detectable concentration (P') is reached. If the rise in concentration is steep this second effect will be small. On the other hand, if dilution is great and the ascent of the curve is gradual then the dilution effect will assume importance. The relationship of these various factors can be stated more precisely in mathematical form.

Let V_T equal the total volume of blood between the points of injection and detection. This can be considered as the sum of two component volumes, V_1 and V_2. The first, V_1, is the blood in the vessels and that portion of the heart's blood that will leave with the following systole. The other volume, V_2, is the blood in the lungs plus the portion of the heart's blood not ejected. V_2 is the blood making up the "diluting pool."

The linear component, T_1, of the observed

circulation times (T_0-T_1 in fig. 1) is a function of the cardiac output (C).

$$T_1 = \frac{V_1}{C} \tag{1}$$

The rate at which the pool, V_2, delivers indicator is a function of the quantity of indicator present in V_2. This quantity, Q, is a resultant of two components.

$$Q = A - B \tag{2}$$

when A is the amount of indicator which has entered and B the amount which has left. Then

$$\frac{dQ}{dt} = \frac{dA}{dt} - \frac{dB}{dt} \tag{3}$$

The value $\frac{dA}{dt}$ is a function of the dose, D, of indicator, then

$$\frac{dA}{dt} = kD \tag{4}$$

where k is a constant determined by the concentration of indicator in the injecting syringe and the time it takes to empty it.

The rate at which the indicator leaves the pool is a function of the cardiac output (C) and the concentration as it leaves the pool (P), so

$$\frac{dB}{dt} = CP \tag{5}$$

Since P is the pool concentration it is by definition $\frac{Q}{V_2}$, and

$$\frac{dP}{dt} = \frac{1}{V_2} \cdot \frac{dQ}{dt} \tag{6}$$

By substituting equations (4), (5) and (6) in equation 3

$$\frac{dP}{dt} = \frac{kD - CP}{V_2} \tag{7}$$

This can be integrated into the form

$$T_2 = \frac{V_2}{C} \ln \frac{kD}{kD - CP'} \tag{8}$$

where T_2 is the time from the appearance of the first particle of indicator (T_1) until the time (T_2) when a detectable concentration (P') is reached.

Then the total observed circulation time is the sum of T_1 and T_2 or

$$T = \frac{V_1}{C} + \frac{V_2}{C} \ln \frac{kD}{kD - CP'} \tag{9}$$

If this exponential effect is significant, then diminishing the amount of indicator used should prolong the observed circulation time as shown in figure 3. On the other hand, if only the linear relationship holds, changing the dose should not change the circulation time. In order to establish this hypothesis, 33 experiments were performed to study the effect of diminishing the dose of indicator on the observed circulation time.

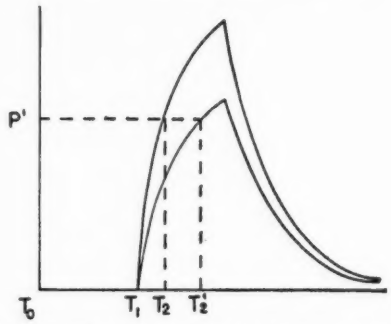


FIG. 3. Effect of diminishing dose of indicator on circulation time.

METHODS

The circulation times were performed with the patients lying as flat in bed as was comfortable with the arm approximately at heart level. No attempt was made to have the patients in a basal state since each experiment served as its own control. The largest vein in the antecubital fossa was selected and 5 ml. of either 10 per cent or 20 per cent Decholin were rapidly injected through an 18 gage needle. An attempt was made to push the plunger into the syringe at the same rate in each injection. The patients were asked to signify both the onset and disappearance of the bitter taste, and times were noted on a stopwatch. After waiting a few minutes the test was again performed, using that concentration of Decholin not used in the first injection. After waiting another few minutes, in 21 cases the first dose was repeated. It was discovered that it made little difference which concentration was used first nor

TABLE 1.—*Comparison of Twenty Per Cent and Ten Per Cent Circulation Time in Patients with Congestive Heart Failure and Normal Subjects*

	Onset of Taste (seconds)		Duration of Taste (seconds)		$\left(\frac{\text{Trans. card. diam.}}{\text{intrathor. diam.}}\right)^2$
	20% Decholin	10% Decholin	20% Decholin	10% Decholin	
Patients with Failure					
L.P.	31	36	24	21	0.413
F.E.J.	27	26	16	8	0.089
H.B.H.	25	32	16	11	0.196
E.E.C.	31	39	19	8	0.140
C.A.G.	20	26	24	13	0.341
M.M.	24	29	22	16	0.277
R.R.	26	36	11	8	0.265
J.M.	33	39	20	12	0.282
C.G.	21	24	15	12	0.137
L.H.	24	33	25	17	0.189
W.H.	18	20	11	9	0.110
A.J.	18	22	32	25	0.227
G.F.	22	—	27	—	0.329
C.H.	40	—	21	—	0.139
R.D.	22	29	25	14	0.133
Patients without Failure					
G.L.	12	12	16	11	—
C.M.	11	9	9	8	—
W.H.	15	16	15	9	—
D.R.	13	13	11	12	—
G.D.H.	11	13	9	7	—
R.B.	14	18	8	11	0.0535
E.W.	17	17	23	23	0.0602
G.Mc.	17	18	14	7	0.0795
H.R.	13	14	11	6	0.0621
G.M.	10	12	13	10	0.0482
J.Bu.	10	12	10	9	0.0490
G.S.	16	19	13	9	0.0340
H.S.	12	13	23	19	0.0315
D.C.	16	24	8	4	0.0752
F.V.	10	11	6	5	0.193
J.B.	18	19	17	14	0.0887
K.M.	13	14	9	7	0.157
C.W.	15	18	20	14	0.115

was there any consistent or significant difference in the first and third measurements. Presumably dilution and excretion reduce the blood level of Decholin so rapidly that the remainder after two or three minutes does not form any appreciable increment. Cardiac and intrathoracic diameters were determined from standard 6 foot chest films.

RESULTS

The results are presented in table 1. The taste onset was faster with 20 per cent Decholin than with 10 per cent, and this difference was greater in cardiac patients with failure than in patients without failure. The duration of taste was longer with 20 per cent Decholin, and,

TABLE 2.—*Measured Differences*

Difference Measured	Mean	Probability Measurement
	Seconds	
Difference in taste onset between doses in all subjects	2.6	<0.001
Difference in taste duration between doses in all subjects	4.4	<0.001
Increased difference in failure patients of taste onset between doses	4.2	<0.001
Increased difference in failure patients of taste duration between doses	3.8	<0.01

again, this difference was greater in patients with failure. These differences as well as the probability of obtaining them by chance are presented in table 2. In these experiments the correlation between circulation time and heart volume as expressed by the ratio (transverse cardiac diameters/intrathoracic diameter)[3] is fair (Bravais-Pearson coefficient of correlation = 0.63).

Discussion

From these preliminary experiments the tentative conclusion is drawn that the "pooling" effect is one of the factors controlling the observed circulation time. Currently a method is being sought for a suitable method for the continuous recording of time-concentration curves following the injection of an indicator. The equation (9) presented probably is not an exact description of the factors controlling circulation time. For example, V_1 and V_2 are not necessarily distinct quantities, and for the purpose of simplification there is the *ad hoc* assumption that the time it takes a single rapid particle to traverse the "pool" is very short in comparison with the total circulation time. However, it is thought that the equation gives a good approximate description of the parameters involved. The fair correlation between heart volume and circulation time in this report is only partially in agreement with the work of Meneely and Chesnut.[8] However, it must be rememberd that the heart is only a part of the diluting system. The lungs are probably the more important member. Morever, it is likely that the linear component $\frac{V_1}{C}$ consumes the major portion of the observed time interval.

Summary

Circulation time is defined as the time that it takes an injected indicator to reach a detectable concentration at the place of detection. A discussion of the factors affecting circulation time is presented with a mathematical analysis. By injecting various amounts of indicator it has been shown that "pooling," an exponential parameter previously not well defined, is one of the factors determining circulation time.

Acknowledgment

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Observations Concerning the Metabolism of Cholesterol in the Hypo- and Hyperthyroid Rat

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(With the technical assistance of Eichi Shibata, B.S.)

The administration of thiouracil induced a rise and administration of thyroid substance a decrease of the plasma cholesterol concentration in rats. The concentration and daily output of bile cholesterol was markedly reduced in hypothyroid rats and markedly increased in hyperthyroid rats. Evidence is presented which suggests that the rate of synthesis of cholesterol is significantly increased in the hyperthyroid rat and decreased in the hypothyroid rat.

AN INVERSE relationship between the plasma cholesterol concentration and the level of thyroid activity has long been recognized.[1] Although this relationship is not quantitative,[2] in general, hyperthyroidism is associated with a decrease, and hypothyroidism with an increase, in the plasma cholesterol concentration.[3, 4] The underlying mechanism has not as yet been clarified.

Preliminary studies from this laboratory[5] have shown a disturbance of biliary excretion of cholesterol in rats with deranged thyroid activity. The striking increase in concentration and daily output of cholesterol that was found in the bile of rats with induced hyperthyroidism suggested that this state was associated with an increased rate of hepatic synthesis of cholesterol. Conversely, the markedly decreased biliary cholesterol output in hypothyroid rats suggested a decreased rate of hepatic synthesis of cholesterol. The present studies were undertaken to test the validity of this hypothesis.

METHODS

Two separate series of rats were fed either thiouracil* or powdered thyroid substance in their diet. The first series of 8 week old male rats (Long-Evans) consisted of (a) animals fed 0.25 per cent thiouracil in their food for 33 days, (b) rats fed 0.12 per cent powdered thyroid substance in their diet for 18 days, and (c) control rats maintained on ordinary stock diet. The second series of 13 week old rats was followed for 42 days. It consisted of (a) rats maintained on 0.3 per cent thiouracil, (b) rats maintained on 0.3 per cent thyroid substance, and (c) control rats. The results obtained on the plasma and bile contents of cholesterol were essentially similar in the two series and accordingly have been grouped together.

Cannulation of the bile duct, 24-hour collection and analysis of bile for cholesterol were accomplished according to previously described methods.[6, 7] Food was withheld from all rats during such bile collections. Data concerning rat bile were accepted only if autopsy examination indicated that there had been neither rupture nor obstruction of the bile duct.

Data on the rate of accumulation of cholesterol in plasma[8, 9] in the experimental animals were obtained by analyses of the plasma for cholesterol before and 24 hours after biliary obstruction.

Study of the rate of disappearance of cholesterol from plasma was accomplished in both the hypo- and hyperthyroid rat by the measurement of the plasma cholesterol in each rat immediately, 1, 3, 6, 12, and 24 hours after the intravenous injection of 2 cc. of hypercholesteremic rat plasma (950 mg. per 100 cc.). The latter was prepared as described previously.[13]

RESULTS

A. Production of Hypo- and Hyperthyroidism in Rats

The administration of thiouracil and powdered thyroid substance was found, as already described,[12] to produce hypo- and hyperthyroidism, respectively, in our rats. The weight gain was greatest in the control and least in

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the hyperthyroid rats (table 1). No untoward manifestations other than retarded growth and decreased activity were observed in the rats receiving thiouracil. The rats given thyroid content of 41 rats made hyperthyroid fell from 50.4 to 40 mg. per 100 cc. No significant change occurred in the plasma of 29 control rats. The decreased total cholesterol concentration in

TABLE 1.—*The Changes in Average Plasma Cholesterol Concentration after Production of Hypo- and Hyperthyroidism*

Type of Rat	No. of Rats	Weight (Gm.)		Plasma Cholesterol Concentration (mg./100 cc.)					
		Before Medication	After Medication	Before Medication			After Medication		
				Total	Free	Ester	Total	Free	Ester
Control	29	215	262	54 (S.E.M. ±1.8)*	5.9	48.1	54 (S.E.M. ±2.4)	7.2	46.8
Hypothyroid	45	201	227	47.3 (S.E.M. ±1.2)	4.5	42.8	67.2 (S.E.M. ±1.6)	13	54.2
Hyperthyroid	41	196	212	50.4 (S.E.M. ±1.6)	7	43.4	40 (S.E.M. ±1.3)	6.6	33.4

* S.E.M. = standard error of the mean.

TABLE 2.—*The Average Concentration and Daily Output of Bile Cholesterol in Hypo- and Hyperthyroid Rats*

Type of Rat	No. of Rats	Bile		
		Volume	Cholesterol	
			Concentration	Content
		cc./24 hrs.	*mg./100 cc.*	*mg./24 hrs.*
Control	16	13.2	20.7 (S.E.M. ±1.5)*	2.7 (S.E.M. ±0.14)
Hypothyroid	17	12	9.8 (S.E.M. ±0.8)	1.2 (S.E.M. ±0.11)
Hyperthyroid	17	13.3	42.1 (S.E.M. ±3.1)	5.6 (S.E.M. ±0.56)

* S.E.M. = standard error of the mean.

substance exhibited hyperactivity, marked tremor, tachycardia, and poor weight gain, despite a significant polyphagia.

Histologic examination of the thyroid glands from representative examples of each group revealed changes closely resembling those described by Karp and Stetten.[12]

B. Changes in the Plasma Cholesterol Concentration of Hypo- and Hyperthyroid Rats

Both the free and esterified cholesterol content of plasma rose (table 1) in those rats made hypothyroid. The average plasma total cholesterol content in 45 rats thus rose from 47.3 mg. per 100 cc. before thiouracil administration to 67.2 mg. per 100 cc. Conversely, (table 1), the average plasma total cholesterol the hyperthyroid rats was due largely to a decrease in the ester fraction.

C. Changes in Excretion of Biliary Cholesterol in Hypo- and Hyperthyroid Rats

In strong contrast to the change observed in plasma, the cholesterol content of the bile of the hypothyroid rat was significantly reduced. Thus, the average daily biliary excretion of cholesterol in 17 hypothyroid rats was 1.1 mg., compared with the average excretion of 2.6 mg. found in 16 control animals (table 2). The diminution observed in the hypothyroid rats was due to a reduction in biliary concentration of cholesterol (table 2), the volume of bile being approximately unchanged.

On the other hand, 17 hyperthyroid rats

were found to excrete an average of 5.6 mg. of cholesterol in their bile per day (table 2). This increase in excretion was found also to be due primarily to an increase in the biliary concentration of cholesterol rather than in the total volume of bile excreted.

TABLE 3.—*Changes in Average Plasma Cholesterol Concentration after Bile Duct Ligation in Hypo- and Hyperthyroid Rats*

Type of Rat	No. of Rats	Average Plasma Cholesterol Concentration (mg./100 cc.)						
		Before Ligation			24 Hours After Ligation			Net Increase After Ligation, Total
		Total	Free	Ester	Total	Free	Ester	
								mg./100 cc.
Control	11	47.5	6.7	40.8	119 (S.E.M. ±3.2)*	49.3	69.7	72 (S.E.M. ±3.9)
Hypothyroid	19	65.6	12.3	53.3	115 (S.E.M. ±4.1)	46.2	68.8	49 (S.E.M. ±6.4)
Hyperthyroid	21	37.6	7.1	30.5	147 (S.E.M. ±8.7)	78.6	68.4	109 (S.E.M. ±9.0)

* S.E.M. = standard error of the mean.

TABLE 4.—*Rate of Disappearance of Injected Cholesterol in Hypo- and Hyperthyroid Rats**

Type of Rat	No. of Rats	Plasma Cholesterol Increments (mg./100 cc.)†				
		Immediately After Injection	1 Hour After Injection	3 Hours After Injection	6 Hours After Injection	12 Hours After Injection
Control	5	114 (S.E. Mean: ±5.4)	113‡	69.6 (S.E. Mean: ±3.4)	33 (S.E. Mean: ±3.5)	9 (S.E. Mean: ±3.5)
Hyperthyroid	7	137 (S.E. Mean: ±7)	103 (S.E. Mean: ±6.5)	58.4 (S.E. Mean: ±8)	6 (S.E. Mean: ±4.1)	−18 (S.E. Mean: ±7.4)
Hypothyroid	6	127.6 (S.E. Mean: ±8.4)	118 (S.E. Mean: ±3.4)	90 (S.E. Mean: ±6.3)	51.5 (S.E. Mean: ±9)	10.8 (S.E. Mean: ±4.4)

* Hypercholesteremia was induced by intravenous injection of hypercholesteremic rat plasma.[13]
† These increments represent the plasma cholesterol (mg. per 100 cc.) in *excess* of the preinjection values.
‡ Number of rats too small to permit calculation of the standard error.

D. Changes in Plasma Cholesterol Content after Biliary Obstruction in Hypo- and Hyperthyroid Rats

Following the induction of biliary obstruction, the liver of the rat apparently discharges excess cholesterol at a constant rate into the plasma.[8, 9] Therefore, it was thought desirable to study the rate of such discharge in both the hypo- and hyperthyroid animal. Biliary obstruction was produced in 11 control, 19 hypo-, and 21 hyperthyroid rats. The average plasma cholesterol content of the control rats increased approximately 72 mg. per 100 cc. in 24 hours (47.5 to 119 mg. per 100 cc.). (See table 3.) The average increase in the hypothyroid rats was considerably less, being approximately 49 mg. per 100 cc. (65.6 to 115 mg. per 100 cc.). On the other hand, an average increase of 109 mg. per 100 cc. (37.6 to 147 mg. per 100 cc.) occurred in the plasma cholesterol content of the hyperthyroid rats. These results, of course, suggested (a) that the liver of the hyperthyroid rat was either manufacturing or discharging cholesterol into plasma at a far faster rate, or (b) that there was a marked decrease in the rate of destruction or excretion of the cholesterol in plasma. Exactly converse mechanisms were suggested to occur in the hypothyroid rat.

E. The Rate of Disappearance of Parenterally Administered Cholesterol in Hypo- and Hyperthyroid Rats

In view of the above results, it appeared necessary to determine whether a change in the rate of destruction or excretion of plasma cholesterol occurred in the hypo- and hyperthyroid animal. Therefore, excess cholesterol (approximately 19 mg.) in the form of hypercholesteremic rat plasma[13, 14] was given intravenously to rats with deranged and normal thyroid activity and the rate of its disappearance from plasma was studied. It was found (see table 4) that following such injection an immediate hypercholesteremia of not very different degree occurred in the eu-, hypo-, and hyperthyroid rats. However, a far faster rate of disappearance of this injected cholesterol was observed in the hyperthyroid rat. Thus, although no significant change had occurred in the plasma cholesterol concentration of both the eu- and hypothyroid rats one hour after injection, the cholesterol content had fallen 30 mg. per 100 cc. in the hyperthyroid rat. Moreover, after six hours, the abnormal cholesterol content had disappeared almost completely from the blood of the hyperthyroid rat, although a similar disappearance was not observed in the control and hypothyroid rats until some time between 12 and 24 hours after injection. These results indicated that the hyperthyroid rat was able to rid his plasma far more quickly of excess cholesterol than either the eu- or hypothyroid animal. The results also suggested strongly that the previously observed abnormally rapid rate of cholesterol accumulation in the blood of the hyperthyroid rat, after biliary obstruction, could only be due to increased hepatic discharge of cholesterol into plasma.

Discussion

The foregoing studies demonstrate that hyperthyroidism induces a consistent decrease, and hypothyroidism, a consistent increase in the plasma cholesterol concentration of the rat. When the duration of the drug administration is more prolonged, the magnitude of such changes may be considerably greater than those observed here.[10, 11] The decreased plasma concentration observed in the hyperthyroid state might conceivably follow a more rapid rate of destruction, excretion, or tissue deposition of cholesterol, or it might result from a depressed rate of cholesterol synthesis. The converse possibilities are to be considered in the hypothyroid state.

Besides these expected changes in the plasma content of cholesterol of rats suffering from deranged thyroid activity, we also have found other evidences of disturbed cholesterol metabolism. Thus, the biliary excretion of cholesterol was found increased in hyper- and decreased in hypothyroidism despite variations in the opposite direction of the plasma cholesterol in these two states. Moreover, the amount of cholesterol excreted in the bile of many of the hyperthyroid rats was great enough to suggest the possibility that this type of rat must synthesize cholesterol at a more rapid rate than the eu- or hypothyroid rat.

This latter possibility was verified in the subsequent experiments in which the hyperthyroid rat was found to accumulate cholesterol in his plasma more rapidly after biliary obstruction than the eu- or hypothyroid rat. Moreover, this process of accumulation was not found due to a diminished rate of elimination or destruction of plasma cholesterol. This last finding, of course, suggested that the excess accumulation was due to an increase in rate of cholesterol synthesis. This increased rate undoubtedly occurs in the liver, in view of the fact that previous studies from this laboratory[9, 15] have demonstrated that the liver is the chief, if not the sole, source of plasma cholesterol. A decreased rate, on the other hand, occurs in the hypothyroid state. The data obtained in these studies are consistent with the observations of Karp and Stetten[12] on the rate of deuterium incorporation into the hepatic sterol content of rats with deranged thyroid metabolism.

Whether increased intestinal excretion or increased destruction of cholesterol precedes, accompanies, or follows the increased rate of hepatic manufacture of cholesterol in hyperthyroidism cannot be determined at this time with certainty. It should be pointed out, however, that the existence of the relatively low

blood cholesterol in this state and the reverse in hypothyroidism, suggests that the initial change may be one involving the rate of elimination or destruction of cholesterol from the blood and tissues of the animal.

The reciprocal relationship observed between the biliary output of cholesterol and the plasma content of the same substance in the two states of thyroid derangement, of course, has intrigued us. It might be considered, at first glance, that excessive biliary excretion of cholesterol observed in hyperthyroidism might be responsible for the low plasma cholesterol; however, other studies of ours[10] have indicated that the excretion of biliary cholesterol bears no relation to the plasma level of cholesterol.

The increased cholesterol content of bile in hyperthyroid rats may be a reflection, in some manner, of the already demonstrated increased rate of hepatic synthesis or discharge of cholesterol. The converse, of course, might be true in hypothyroidism. Studies relating to this are now in progress.

Summary

The administration of thiouracil induced a significant rise and thyroid substance a significant decrease of the plasma cholesterol concentration in rats.

The concentration and daily output of cholesterol was considerably reduced in the bile of hypothyroid rats and markedly increased in the bile of hyperthyroid rats.

The hyperthyroid rat was found to accumulate cholesterol in his plasma after biliary obstruction much more rapidly than the eu- or hypothyroid rat. This accumulation was found to be due to a far more rapid rate of manufacture or discharge of cholesterol by the liver of the hyperthyroid rat. The converse was found in the hypothyroid rat.

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Tissue Clearance as a Measure of Nutritive Blood Flow and the Effect of Lumbar Sympathetic Block upon Such Measures in Calf Muscle

By SAMUEL I. RAPAPORT, M.D., ALBERT SAUL, B.S., CHESTER HYMAN, PH.D., AND M. E. MORTON, PH.D., M.D.

This paper reports the effect of procedures known to alter local blood flow upon the rate of removal of locally injected Na^{24} and I^{131}. An evaluation of this clearance method as a measure of nutritive blood flow is made. A second purpose is to report the lack of effect upon clearance from calf muscle of lumbar sympathetic block, and to discuss its therapeutic implications.

THE rate of disappearance of a locally injected radioactive isotope has been proposed as a measure of effective or nutritive blood flow through that part.[1–3] This paper reports experiments designed to clarify the value and limitations of this method of measurement, by noting the effect upon clearance of technics known to alter local blood flow, namely, reactive hyperemia, increased venous pressure, and the release of sympathetic tone in the distal skin by reflex heating. The method was then used to assess the effect of lumbar sympathetic block upon clearance from resting calf muscle. These latter observations are emphasized because such information about the result of sympathetic nerve interruption upon muscle blood flow helps one to understand what may be expected of lumbar sympathectomy in the treatment of peripheral vascular disease.

The problem of whether or not the blood vessels of resting skeletal muscle are maintained in a state of partial constriction by sympathetic vasomotor impulses has been attacked by many investigators. Evidence from animal investigation suggests the existence of such vasoconstrictor tone.[4–7] The results of observations in man are less consistent. Friedlander and co-workers[8] found that deep muscle temperature fell after sympathetic interruption and so concluded that vasoconstrictor tone does not exist. Grant and Pearson[9] could not demonstrate a significant increase in forearm blood flow after moderate reflex heating. Smith and his co-workers,[10] in an analysis of the effect of spinal anesthetic upon blood pressure, concluded that there is negligible tonic sympathetic activity in skeletal muscle. Measurements, weeks and months after surgery, by various workers[9, 11, 12] have shown that muscle blood flow is not increased by sympathectomy; however, vasodilatation immediately after sympathetic interruption remains a possibility, since denervated vessels soon regain intrinsic tone.

On the other hand, most plethysmographic data support the existence of vasoconstrictor tone in muscle vessels. Wilkins and Eichna[11] found that warming the body increased forearm blood flow from two- to fourfold. Barcroft and his co-workers[13, 14] reported a similar increase in forearm blood flow after the release of sympathetic tone by nerve block or by reflex heating. They showed this to be due to increased flow through the underlying muscle and not the skin. The case for the existence of vasoconstrictor tone in muscle vessels in man

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has been convincingly summarized by Barcroft and Edholm.[15]

There are recent reports in which the clearance technic has been used to evaluate the effect of general vasodilator drugs on calf muscle blood flow. A decrease in the rate of removal of radioactive sodium (Na^{24}) has been described after the administration of Priscoline.[16,17] Reflex heating plus tetraethylammonium chloride produced no significant change in the clearance rate.[18] These results, however, do not necessarily indicate an absence of vasoconstrictor tone, since some dilatation of the muscle vessels could be masked by a shift of blood to areas more widely dilated by these agents.

We have examined the result of lumbar sympathetic block upon the rate of removal of radioactive iodine (I^{131}) or Na^{24} from calf muscle in 10 patients. In addition, the effect of the block upon blood flow through the toe tip was determined by skin temperature measurements and venous occlusion plethysmography. This permitted a comparison of the result of the block upon nutritive muscle blood flow estimated by clearance, with its effect upon blood flow through the toe, an area known to be under dominant sympathetic nervous system control.

Method

Clearance is measured by injection into the region to be studied of several microcuries of Na^{24} or I^{131} as ions in a small amount of saline. These ions can be used interchangeably, since we have shown that in man they are cleared at the same rate.[19] A GM counter is placed next to the skin overlying the site of injection and the external counting rate is continuously recorded. The theoretic basis for the method and the details of the technic have been described by Kety,[1] who showed that when blood flow is constant, a constant fraction of the labeled extracellular ion is cleared per unit time. A plot of the log of external counts per minute against time will give a straight line of negative slope, k, which is the clearance rate and may be expressed as per cent of the ion removed per minute. Rates of removal may also be expressed as the half time, $t_{\frac{1}{2}}$, which is the number of minutes taken for the external counting rate to be halved.

All blood flow measurements were made from the second toe by the use of a Burch-Winsor pneumoplethysmograph[20] and the venous occlusion method as described by Goetz.[21] Temperatures were measured by a thermocouple and recorded upon a self balancing potentiometer (Micromax).

In the experiments on the effect of lumbar sympathetic block, the patient, lightly clad, rested quietly in the supine position. An attempt was made to have the room cool; most of the experiments were started with a room temperature between 65 and 70 F., in two it was about 75 F., and in one it was 87 F. Room temperature usually increased 2 to 3 F. during the course of the experiment. After about 30 minutes of rest, two or more measurements of toe blood flow were made. Then from 2.5 to 18 microcuries of Na^{24} or I^{131} in from 0.05 to 0.80 cc. of isotonic saline were injected into the calf muscle. A gamma-sensitive counter was placed next to the skin overlying the site of injection, and its output was inscribed by a pen activated from the relay of a Tracerlab autoscaler. The external counting rate was recorded for from about 10 to 15 minutes and then toe blood flow was measured again. After this the patient was turned on his side and the lumbar sympathetic ganglions were blocked with procaine. In almost every instance 5 to 15 minutes were required until the beginning rise in toe temperature indicated that a block had been obtained. The patient was then turned onto his back and a second determination of clearance was made over a 10 to 20 minute period. In about half the patients it was necessary to make a second injection at this time because of a low counting rate. Toe blood flow measurements were also made before and after the second clearance determination to establish the persistance of the block.

The experiments on the release of sympathetic tone in the distal skin by reflex heating were done in a similar fashion. The subject rested, almost nude, in a cool room (67 to 73 F.) until toe temperature stabilized at about room temperature. Clearance rates were taken from the subcutaneous tissues at the base of the second toe and blood flow measurements from the tip of the second toe. Na^{24} measured by a thin-walled beta counter was used in most of these experiments. The body was heated by a "baker" placed over the trunk. After 45 minutes to an hour of heat, when toe temperature had risen and leveled off, the blood flow and clearance determinations were repeated.

Results and Discussion

Since any difference between resting muscle clearance and clearance after sympathetic block was to be taken as evidence of an alteration in blood flow produced by the block, it was necessary to establish the fact that clearance did not change spontaneously. On 13 occasions, resting muscle clearance was measured for a 30 minute period. It was found necessary to discard the data of the first two or three minutes after

the injection, since the injected ion frequently did not begin to leave the site during this period. A straight line of constant slope could be fitted to the data obtained throughout the remainder of the period in every instance except one. In the exception, a break in the slope occurred at the end of 12 minutes and a second slope was established which persisted until the end of the determination. Whether this was due to a spontaneous change in muscle blood flow cannot be said. In a large number of clearance determinations made from the subcutaneous tissues of the forearm, for periods

TABLE 1.—*The Effect of Reactive Hyperemia upon Clearance from Calf Muscle*

Subject	Age	Room Temp. °F.	Resting Clearance K', %/min.	Reactive Hyperemia Clearance, K'' %/min.	$\frac{K''}{K'}$
P. G.	28	61–68	1.7	24.3	14
A. M. S.	24	64–69	4.1	53.6	13
A. S.	26	59–63	4.9	20.6	4.2
D. C.	29	62–64	5.8	64.0	12
R. P.	29	—	6.3	21.7	3.4
Average.....			4.6	36.8	8

usually of 30 minutes but occasionally up to an hour, the data, with rare exceptions, give straight lines with no change of slope over the experimental period.

The next step was to demonstrate the extent of change in muscle clearance produced by changes in muscle blood flow. Kety[1] had shown that reactive hyperemia resulted in a considerable increase in clearance over control levels. We repeated this experiment to obtain additional clearance values to compare with the plethysmographically determined increase in calf muscle blood flow reported by Eichna and Wilkins.[22] They found that, following an arterial occlusion of five minutes, blood flow increased to 14 to 38 cc. per 100 cc. of part per minute (average 23 cc.) which is a ten- to twentyfold increase over resting muscle blood flow. The maximum blood flow is the same after a 5 or 10 minute period of occlusion. The period of marked hyperemia is transient and flow begins to decrease almost immediately after the circulation is reestablished. Grant[23] reports an experiment in which the flow rate may be seen to return almost to the resting level in one minute. Kondo, Winsor and associates[24] describe a return to near control values by the third minute following occlusion of the circulation to the toe for five minutes. Thus it becomes apparent that, if clearance parallels blood flow, a semilogarithmic plot of the counting rate at successive half minute intervals following the release of an arterial tourniquet should not be a straight line but a curve with an initial steep portion followed by a gradual return to the control slope.

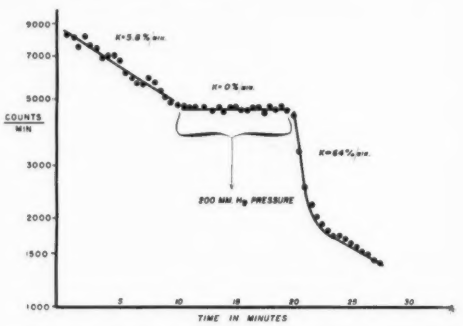


FIG. 1. Effect of reactive hyperemia on muscle clearance of I^{131}.

In several normal subjects, rested in a cool room, clearance from calf muscle ranged from 2 to 6 per cent per minute. Reactive hyperemia was produced by a 10 minute arterial occlusion. A plot of the log of the counting rate obtained when the circulation was reestablished against time, was a curve for several minutes. A straight line could be fitted to the initial points of the curve during the first one to two minutes, and the slope of this line was called the "reactive hyperemia clearance rate."

These rates are summarized in table 1 and a representative experiment is shown in figure 1. One sees that the clearance after arterial occlusion is increased from resting values of 2 to 6 per cent (average 4.6 per cent) to 20 to 60 per cent per minute (average 36.9 per cent). In different subjects the increase ranged from three and one-half to fourteenfold (average eightfold). In comparing these values with the magnitude of the blood flow increase as measured plethysmographically, one must keep in

mind that the plethysmographic values are maximum values taken from repeated determinations made during the first 30 seconds after the circulation is released; whereas the clearance rates represent average blood flows estimated from successive counting rates over half-minute intervals. Therefore we feel the data are evidence that clearance reflects blood flow through muscle. It is also obvious, however, that the clearance technic as used in these experiments is not applicable to the measurement of very rapid changes in blood flow, since average counting rates over about one-half minute were used, and several points were necessary to obtain an accurate slope.

In a recent publication Miller and Wilson[25] have objected to the use of reactive hyperemia experiments on the grounds that during the period of arterial occlusion radioactive ions are accumulating in the local capillaries; and on return of the circulation an unusually high concentration is swept away. They argue that this, rather than increased blood flow, may be the reason for the increase in clearance. This does not seem valid to us. Blood stagnant in the local capillaries about the injection site would be replaced by fresh blood within about 10 seconds at the most. This may be inferred from the observations of Lewis, Pickering and Rothschild,[26] who clearly showed that pain due to the accumulation of local metabolites during ischemic exercise is often relieved within two to four seconds after the circulation is reestablished. Thus, our slopes of reactive hyperemia clearance, which are fitted through at least two successive half-minute counting rates after the release of the circulation, could not be due to the removal of blood overly saturated with the radioactive ion.

TABLE 2.—*The Effect of Increased Venous Pressure upon Clearance*

Subject	Age	Diagnosis	Site	Venous Pressure mm. Hg	Control K′, %/min.	Venous Pressure K″, %/min.	Post-Venous Pressure K‴, %/min.
F. F.	61	Cerebral arteriosclerosis	I. M.	50	10.4	4.3	12.4
W. B.	54	Bronchogenic carcinoma	I. M.	50	5.4	1.7	5.8
J. P.	59	Arteriosclerosis obliterans	I. M.	50	3.2	1.4	1.7
S. E.	59	Arteriosclerosis obliterans	Subcut.	35	3.7	0.5	3.3
R. M.	55	Arteriosclerosis obliterans	Subcut.	35	5.6	2.0	6.8
H. F.	29	No known disease	Subcut.	50	6.3	5.9	6.9

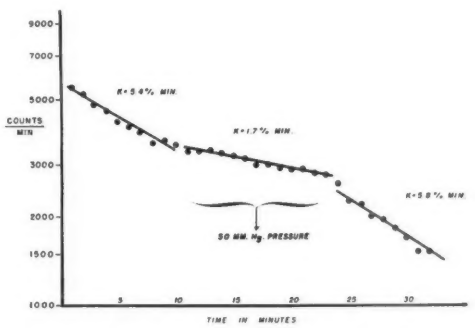


FIG. 2. Effect of increased venous pressure upon muscle clearance of Na^{24}.

Data were also obtained which illustrate the effect of a decrease in blood flow upon resting clearance rates. In several subjects clearance was measured before, during and after a period of elevated venous pressure produced by a proximal pressure cuff at 35 or 50 mm. Hg. These values are collected in table 2 and a single experiment is graphed in figure 2. In all subjects except H. F., the measured muscle or subcutaneous clearances were definitely decreased by raising venous pressure. These results could be explained either by the assumption that the transcapillary diffusion rate is

decreased by an elevated capillary hydrostatic pressure, or, alternatively, by the assumption that blood flow is decreased. Landis[27] has stressed the fact that the diffusion rate of a small ion is independent of "filtration" across the capillary wall. We have shown this for ourselves by a comparison of the clearance rate of Na^{24} or I^{131} when injected in hypertonic albumin and, simultaneously, in a comparable contralateral site, in isotonic saline. The hypertonic albumin produces an outpouring of fluid from the capillaries and a noticeable swelling of the injection site, yet no statistically significant difference was found in the clearance from the two sites. Therefore, if diffusion rates are not significantly altered by filtration, the decrease in clearance produced by a raised venous pressure reflects a decrease in blood flow. That blood flow *is* significantly reduced by an elevation of venous pressure has been shown by gasometric and plethysmographic measurements.[28, 29]

We studied next the effect of reflex heating upon clearance from the distal skin. This procedure, when performed on a previously cooled subject, will result in a large rise in blood flow. This will be due to both an increased capillary blood flow, and the opening of arteriovenous shunts in the toes. The increased capillary flow increased the rate of removal of a labeled ion, but blood shunted through arteriovenous channels would not be expected to increase clearance.

Figure 3 is a record of such an experiment. The upper portion of the figure is a plot of clearance measured from the subcutaneous tissues of the dorsum of the foot at the base of the second toe before and after reflex heating. The lower portion shows typical venous occlusion plethysmographic tracings obtained from the tip of the toe during these periods. Before heating there was no measurable flow through the toe and no movement of the isotope. Heating resulted in an increase in blood flow to 27 cc. per 100 cc. of part per minute, and of clearance to 5.1 per cent per minute.

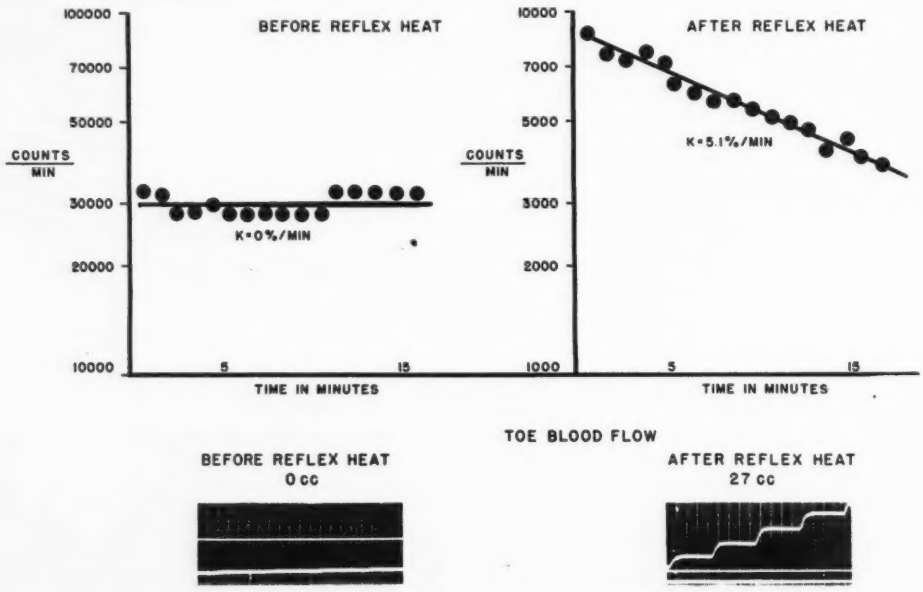


FIG. 3. The effect of reflex heating upon subcutaneous clearance from the dorsum of the foot and blood flow through the toe.

Data from eight experiments are given in table 3, which lists the temperature of the tip of the first toe, blood flow from the second toe, and subcutaneous clearance from the base of

the second toe expressed as per cent per minute. The values for blood flow in this table are averages of at least three determinations. These results clearly demonstrate that an increased blood flow produced by the release of sympathetic tone is accompanied by a large increase in clearance rate. The magnitude of the increase in blood flow is greater than that for clearance. This is to be expected, since after heating total flow through the toe tip includes a large quantity of blood which passes through arteriovenous shunts.

The small values for clearance from the subcutaneous tissues of the foot when the subject was cool are of interest. These ranged in the four well subjects from no movement at all up to 1.5 per cent per minute. They may be compared with the values in table 1 for clearance in resting calf muscle, which averaged 4.6 per cent in five normal subjects. If this average value for clearance from resting muscle reflects a nutritive flow of 1 to 2 cc. per 100 cc. of part per minute, one may readily appreciate the very small blood flow needed to maintain the nutrition of the subcutaneous tissues in a cool environment. None of the subjects noticed any discomfort in their feet; each could have remained indefinitely in the cool environment. The average value in the four normal subjects after reflex heating was 5.4 per cent per minute. We have attempted to produce maximum clearance from the subcutaneous tissues of the hand in resting supine subjects by a combination of reflex heating for one hour, the consumption of 60 cc. of 45 per cent alcohol and direct heating of the hands by a bank of lights for 15 minutes. In 20 measurements, a clearance rate over 10 per cent per minute was obtained five times. The maximum obtained was 13.2 per cent. Values above this in normal subjects have been reached only by applying enough heat to the hands to produce an erythema of the skin for several hours.

Once assured that the release of sympathetic tone in the skin of the foot increased clearance from that site, it was possible to interpret the data obtained from calf muscle before and after lumbar block. These data are summarized in table 4. This table lists the temperature of the big toe before and after the block; the average blood flow through the tip of the second toe before and after each clearance determination; and the clearance from calf muscle, expressed as per cent per minute, determined both before and after the block. Fifteen experiments are given. In the first 10 a definite block was obtained as indicated by a rise in skin temperature and blood flow through the toe. In the last five listed, either the block was missed or arterial occlusion was so severe that the release of sympathetic tone did not significantly increase blood flow through the toe. These experiments may be considered controls, if one assumes that blood flow through the calf could not be altered by sympathetic block without a simultaneous change in blood flow through the toe.

These data show that interruption of the sympathetic supply to the blood vessels of resting calf muscle does not increase nutritive blood flow as measured by clearance. Rather,

TABLE 3.—*The Effect of Reflex Heating upon Blood Flow through and Clearance from the Distal Skin*

Subject	Diagnosis	Room Temp. °F.	Toe Temperature °F.		Blood Flow cc./100cc./min.		Clearance	
			Before Heating	After Heating	Before Heating	After Heating	Before Heating K, %/min.	After Heating, K, %/min.
R. P.	No known vascular disease	70–74	72–73	90–92	3.0	26	0	4.6
F. S.	No known vascular disease	69–70	71–72	90–93	4.5	28	0.7	5.1
F. S.	No known vascular disease	67–69	66–67	82–83	5.5	32	1.5	6.7
T. V.	No known vascular disease	68–69	69–71	91–92	<1	36	0	5.1
L. P.	Vasospasm, after frostbite	73–74	73–74	94–95	<1	44	1.9	7.9
J. S.	Vasospasm, after frostbite	—	—	—	4.5	29	3.1	7.4
C. D.	Arteriosclerosis obliterans	70–74	78–82	90–91	5.0	16	0.6	3.6
R. C.	Diabetes mellitus	75–76	75–76	85–88	4.0	30	4.7	6.5

in all except one of the definite blocks, there was some decrease in postblock clearance; in several patients this was of considerable magnitude; for example, in L. P. it was from 9.5 to 4.1 per cent per minute, in J. S. from 5.8 to 1.5 per cent per minute, and in R. B. from 4.3 to 2.4 per cent per minute. One of the experiments is illustrated in figure 4. One measurement of toe blood flow before block is seen to be 3 cc. per 100 cc. of part per minute. Muscle clearance before block was 3.5 per cent per minute. After the block, toe blood flow increased to 32 cc. but muscle clearance fell to 2.7 per cent. In two of the experiments in which there was no definite evidence of a block, the second clearance was also decreased; in subject R. B. from 3.2 to 2.3 per cent per minute, and in subject J. B. from 3.3 to 2.2 per cent per minute. Therefore, we cannot be sure that the reduced clearance measured after most of the proved blocks was due to the effect of the block, although this would seem likely in the three instances cited in which the decrease after block was large. In any event, there is clear evidence that sympathetic nerve interruption does not *increase* clearance from resting skeletal muscle.

TABLE 4.—*The Effect of Lumbar Sympathetic Block upon Clearance from Calf Muscle*

Subject	Diagnosis	Room Temp. °F.	Toe Temperature °F.		Blood Flow cc./100cc./min.				Clearance	
			Before Block	After Block	Before Block		After Block		Before Block	After Block
					Before K	After K	Before K	After K	K, %/min.	K, %/min.
I. T.	Vasospasm, idiopathic	69–71	74–75	87–89	<1	<1	—	65	8.8	6.1
L. P.	Vasospasm, after cold exposure	76–79	75–76	90–93	<1	<1	42	6.0	9.5	4.9
A. A.	Thrombophlebitis	68–70	78–79	90–93	<1	2.0	27	28	10.7	9.3
W. F.	Thrombophlebitis	87–88	92–93	94–95	35	38	>100	>100	5.6	4.4
A. M.	Persistent pain in feet, etiology undetermined	67–70	69–70	87–88	3.0	3.0	14	32	3.5	2.7
J. S.	Thromboangiitis obliterans	67–73	69–70	90–92	4.0	2.0	46	100	5.8	1.8
J. W.	Arteriosclerosis obliterans	70–74	70–71	89–91	4.0	5.5	23	82	3.5	4.1
J. S.	Arteriosclerosis obliterans	79–82	86–88	90–91	6.5	5.5	18	13	2.6	2.4
R. B.	Arteriosclerosis obliterans	70–76	70–73	85–86	<1	<1	9.5	14	4.3	2.4
R. B.	Arteriosclerosis obliterans	65–66	66–67	88–90	—	—	—	—	3.6	2.1
C. M.	Traumatic aneurysm	—	—	—	7.0	4.0	—	<1	6.5	6.2
J. M.	Arteriosclerosis obliterans	82–83	85–88	87–88	9.5	10	17	17	9.4	8.8
J. E.	Arteriosclerosis obliterans	68–72	74–75	75–75	5.5	6.5	7.5	11	1.1	1.3
R. B.	Arteriosclerosis obliterans	61–67	64–65	66–67	<1	<1	<1	<1	3.2	2.2
J. B.	Arteriosclerosis obliterans	66–73	76–77	77–78	1.0	4.0	2.5	3.5	3.3	2.2

These results are similar to the observations of others[16–18] that vasodilator drugs and reflex heating do not increase clearance from skeletal muscle. However, they do not agree with the plethysmographic measurements of Barcroft and his co-workers,[13] who reported more than a twofold increase in forearm muscle blood

flow after peripheral nerve block. Such a doubling of flow really represents an increase of only about 2 to 3 cc. per 100 cc. of part per minute, yet this rise should produce a corresponding increase in clearance rate.

At this point it is necessary to call attention to two reports which challenge the validity of the clearance technic as a measure of muscle blood flow. Semple and associates[30] doubt the sufficient occlusive disease to prevent a normal resting flow of 1 to 2 cc. per 100 cc. of part per minute. Resting clearance was measured by these workers for 10 minutes. The clearance after exercise was begun within 40 seconds after completion of exercise, but the duration of the measurement which determined the post-exercise clearance value is not given. This would seem important because, just as in the instance

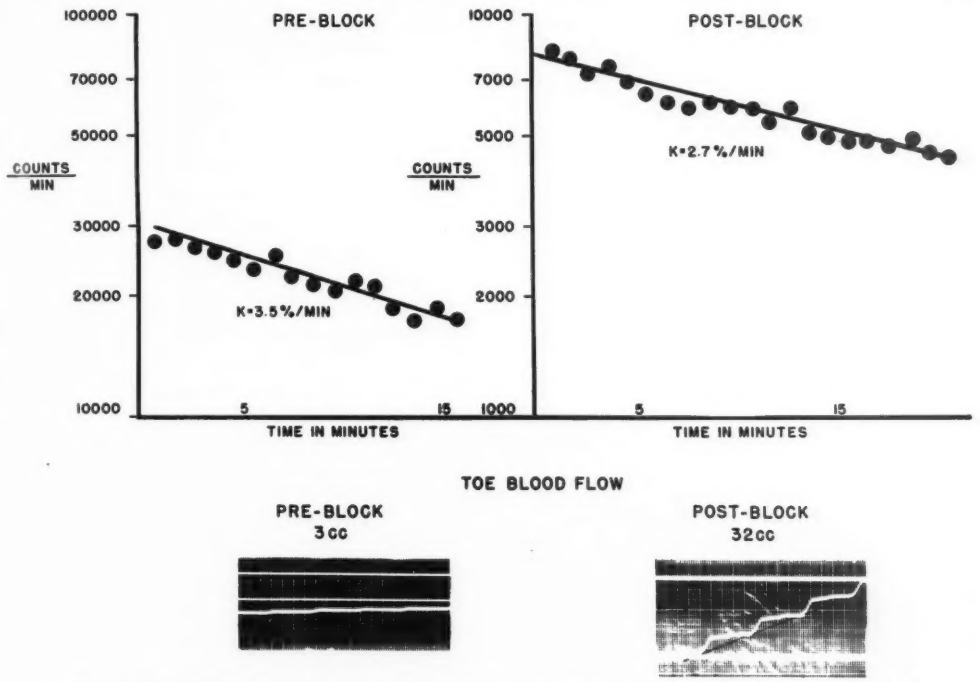


FIG. 4. The effect of lumbar sympathetic block upon clearance from calf muscle and blood flow through the toe.

method because they were unable to find consistent differences between normal subjects and patients with intermittent claudication due to occlusive vascular disease. This was true both for resting values and for the ratio of the rate of removal after exercise to the resting values. There is, in our opinion, very little reason to expect to find a consistent difference in the resting values for the two groups if the criterion for selection of the second group was only the presence of intermittent claudication. The fact that the circulation is insufficient to prevent pain after exercise does not mean that there is of reactive hyperemia, blood flow after exercise does not remain constant but rapidly diminishes. This is seen in Grant's[23] and Shepherd's[31] figures. It is only within the first two to three minutes that there is a large difference between the normal and the patient with intermittent claudication. Except for very strenuous exercise, one would expect that after this time interval, blood flow in the normal subjects would fall within the range obtained in the claudicators. It seems unlikely that averages for plethysmographic values which were begun after two to three minutes would clearly deline-

ate the two groups. Therefore, unless the post-exercise clearances were determined from the rate of removal in the first two to three minutes only, the data of these workers need not discredit the clearance method.

Miller and Wilson[25] have questioned the clearance technic because they were unable to detect an increased clearance from the subcutaneous tissues of the hand or finger after reflex heating sufficient to increase the heat elimination from the hand. It is to be noted, in two of the four experiments they reported, that subcutaneous clearance before reflex heating was greater than 5 per cent per minute. With such an initial clearance rate one suspects that, although the A-V shunts might still be closed, there was little reflex sympathetic constriction of the nutritive supply to the tissues before the heating. In our eight experiments on the effect of reflex heating on the subcutaneous clearance from the dorsum of the foot, particular care was taken to cool the subject thoroughly. Clearance before heating was below 2 per cent in six subjects and below 5 per cent in the other two. A significant rise with heating was obtained without exception.

The second objection of Miller and Wilson, that intravenous adrenaline failed to increase muscle clearance, must be recognized, since Allen and co-workers[32] have shown that a two-fold increase in flow through skeletal muscle will persist during the period of infusion. Therefore, despite the evidence,[1, 2, 33] which our own experiments support, that clearance does parallel blood flow, it remains to be proved specifically that small increases of about 2 to 3 cc. per 100 cc. of part per minute in total muscle blood flow will increase muscle clearance. This is the order of magnitude of the increase Barcroft reported after nerve block. The answer must await simultaneous plethysmographic measurements of muscle blood flow and clearance determinations.

Whether or not the clearance method proved as sensitive as plethysmography, one should remember that a measurement of the rate of removal of a rapidly diffusable ion such as sodium or iodide ion has clinical meaning. For, if some of the materials of muscle metabolism have about the same rates of diffusion, the result of a therapeutic procedure upon clearance is a useful measure of the value of that procedure in improving the nutrition of the muscle. Therefore, our observations on the lack of effect of lumbar sympathetic block upon resting muscle clearance suggest that acute sympathetic interruption is without value as a therapeutic procedure to increase nutritional blood flow to resting skeletal muscle. However, this is rarely the clinical problem, since the patient usually presents an associated arterial insufficiency of the distal skin which may be improved by sympathetic interruption, or else his complaint is of muscle pain on exercise.

There are several clinical reports of large groups of patients[34–39] which discuss the effect of lumbar sympathectomy upon intermittent claudication. These vary in their enthusiasm for the result of the procedure. In general, surgeons have reported that the walking distance of many patients is moderately prolonged, that is, about one-half to three or four blocks. There are some patients who are not helped at all, while an occasional patient is strikingly benefited and may be completely relieved of muscle cramp on ordinary activity. It is difficult to understand how sympathetic interruption can improve intermittent claudication. We have shown that its effect upon muscle blood flow at rest is insufficient to increase the removal rate of a rapidly diffusible small ion. The metabolites which accumulate during exercise or circulatory occlusion are the most profound dilators of muscle vessels. Their action is independent of the sympathetic system. Thus, reactive hyperemia has been shown to be the same before and after preganglionic sympathectomy.[22]

However, it has been suggested that the pain of exercise may be due to circulatory insufficiency which results not so much from the presence of occlusive vascular disease as from added vascular spasm. This has been inferred from the study of an occasional patient in whom, after exercise, the foot may get white and cold and a previously palpable pulse may disappear. Pearl[40] distinguished such patients as having angiospastic claudication and felt it was this group that benefited from sympathetic interruption. Freeman and Montgomery[41] felt

that improvement in claudication time after lumbar sympathetic block indicated the presence of abnormal vasospasm.

There is no evidence that pain produced in well subjects by ischemic exercise is associated with vascular spasm. Rather, the vessels are fully dilated.[26, 31] Furthermore, it has been shown[22] that reactive hyperemia muscle flow is not decreased by sympathetic stimulation which produces vasoconstriction in the distal skin. However, there are two reports which disclose that, in contrast to the normal subject, some patients with occlusive vascular disease may exhibit a decreased blood flow during or immediately after exercise. Lindquist[42] described several patients who showed a marked decrease in oscillometric readings with the onset of muscular cramps. Shepherd[31, 43] who measured calf muscle blood flow plethysmographically after exercise, found a group of patients with arteriosclerosis and claudication in which blood flow after exercise failed to reach a maximum until 1 to 14 minutes after the exercise was stopped. Yet these observations cannot be taken as evidence of sympathetic spasm, since they occur after sympathetic interruption.

Therefore, from the data available at present, it would appear that sympathetic interruption will not increase the effective resting blood flow through skeletal muscle, nor is there evidence that it will improve blood flow after exercise. Rather, the observations of Lindquist[42] and Shepherd[43] indicate that it will not prevent the decreased blood flow after exercise seen in some patients with intermittent claudication. Furthermore, in a careful study, Shepherd[31] could find no increase in blood flow after exercise as a result of sympathetic block. The reason why an occasional patient obtains marked relief of intermittent claudication after lumbar block or lumbar sympathectomy remains obscure.

Summary

This paper is in part a report of the effect of procedures known to alter local blood flow upon clearance of locally injected Na^{24} or I^{131}. The increase with reactive hyperemia has been shown to approach that measured plethysmographically by others. The effect of increased venous pressure is to decrease the rate of removal because it decreases blood flow. The release of sympathetic tone in the distal skin by reflex heating results in a large rise in subcutaneous clearance rate. When these results were established, the clearance method was then used to assess the effect of lumbar sympathetic block upon clearance from calf muscle. No increase in resting muscle clearance was found after lumbar sympathetic block. The relation between the result of lumbar sympathetic block upon muscle blood flow and its clinical effect has been discussed.

Acknowledgments

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The Abnormal Serum Lipid Pattern in Patients with Coronary Arteriosclerosis

By Alfred Steiner, M.D., Forrest E. Kendall, Ph.D., and James A. L. Mathers, M.D.

Studies in experimental arteriosclerosis have indicated that the relative level of serum lipid phosphorus may be as significant a factor as the absolute level of serum cholesterol in the production of arterial lesions. For this reason, the serum lipid pattern of 82 patients with coronary arteriosclerosis has been compared with that of 112 healthy adults. An elevation of the serum cholesterol, serum lipid phosphorus and the serum cholesterol–lipid phosphorus molar ratio has been found in most of the patients with coronary arteriosclerosis.

PREVIOUS studies[1, 2] from this laboratory have demonstrated that the serum cholesterol pattern of patients with coronary arteriosclerosis differs from that of normal individuals in that the serum cholesterol levels are higher and more inconstant than those in control subjects. Recent experimental data have indicated that the ratio between serum cholesterol and serum phospholipids may be as significant as the absolute level of serum cholesterol in the production of arteriosclerosis in animals. A report from this laboratory[3] revealed that in the production of experimental arteriosclerosis in rabbits fed cholesterol or dogs fed cholesterol plus thiouracil, the serum cholesterol levels increased disproportionately to the increase in serum phospholipid. This resulted in an abnormal cholesterol-phospholipid ratio. Kellner and his co-workers[4] have recently shown that the intravenous injection of synthetic detergents in rabbits resulted in an elevation of the serum cholesterol and serum phospholipids. The injection of detergents in cholesterol fed rabbits partially inhibited the development of experimental arteriosclerosis. The protective effect was evident in those animals in which the elevation of serum cholesterol was accompanied by a parallel or disproportionate increase in serum phospholipids. Duff and Payne[5] have reported that the inhibition of experimental cholesterol arteriosclerosis in rabbits with alloxan diabetes is related to a marked increase in serum neutral fat and lipid phosphorus.

It was therefore thought to be of interest to study the serum cholesterol, serum lipid phosphorus and the serum cholesterol–lipid phosphorus ratio in a group of patients with coronary arteriosclerosis to determine if further abnormal patterns of serum lipids existed in this condition. While this project was under way, a report by Gertler and his co-workers[6] presented data and postulated that the levels of serum cholesterol and serum phospholipid are less important in coronary artery disease than is the ratio of cholesterol to phospholipids.

Methods

Two groups of individuals were studied. The first was composed of 82 patients in whom bouts of well documented coronary thrombosis had occurred. Individuals were not included in this group until at least two months had elapsed from the onset of the acute cardiac infarction. There were 20 women and 62 men whose ages varied from 32 to 72 years, the average age being 52 years. The second group consisted of 112 healthy adults varying in age from 23 to 62, the average being 41 years.

Blood was obtained in the nonfasting state. Serum cholesterol determinations were made by the method of Schoenheimer and Sperry.[7] Serum lipid phosphorus was determined by the method of Fiske and Subbarow[8] upon an alcohol-acetone extract of serum. The serum cholesterol–serum lipid phosphorus molar ratio was computed for each individual. The value for the serum phospholipid may be obtained by mul-

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TABLE 1.—*Serum Cholesterol, Serum Lipid Phosphorus, and Molar Ratios in Coronary Arteriosclerosis and Control Subjects*

	Serum Cholesterol mg./100 cc.		Lipid Phosphorus mg./100 cc.		Cholesterol-Lipid Phosphorus Molar Ratio	
	Range	Mean	Range	Mean	Range	Mean
Coronary Arteriosclerosis (82 patients)	174–371	263 ± 44*	7.7–17.6	11.2 ± 1.9	1.52–2.43	1.88 ± 0.18
Control (112 subjects)	118–297	198 ± 33	6.5–12.7	9.3 ± 1.4	1.30–2.09	1.72 ± 0.17

* Standard deviation.

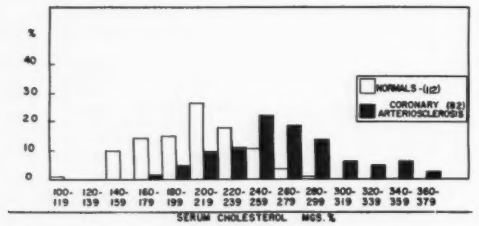


FIG. 1. Distribution of serum cholesterol values.

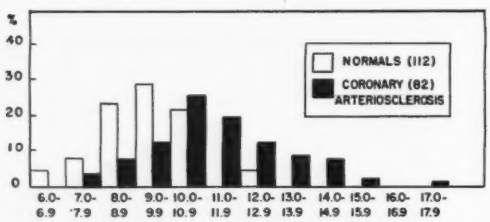


FIG. 2. Distribution of serum lipid phosphorus.

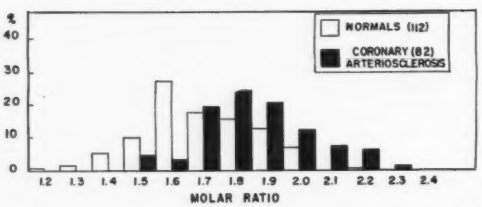


FIG. 3. Distribution of serum cholesterol–lipid phosphorus molar ratios.

tiplying the value for serum lipid phosphorus by the factor of 25.

RESULTS

The range and the average values for the serum cholesterol, lipid phosphorus, and the serum cholesterol–lipid phosphorus molar ratio for the two groups are tabulated in table 1. The serum cholesterol values of the normal subjects varied from 118 to 297 mg. per 100 cc. with a mean of 198 mg. per 100 cc. The serum cholesterol of the patients with coronary arteriosclerosis varied from 174 to 371 mg. per 100 cc. with a mean of 263 mg. per 100 cc. Figure 1 reveals the different distribution curves for serum cholesterol of the patients and the normal subjects.

The serum lipid phosphorus levels of the normal subjects varied from 6.5 to 12.7 mg. per 100 cc., with a mean of 9.3 mg. per 100 cc. for the group. The lipid phosphorus for the patients with coronary arteriosclerosis varied

TABLE 2.—*Serum Cholesterol, Serum Lipid Phosphorus and Molar Ratios in Coronary Arteriosclerosis and Control Subjects*

Age	Coronary Group				Control Group			
	No. Pts.	Aver. Serum Cholest.	Aver. Lipid P	Ser. Chol.–Lipid P Molar Ratio	No. Pts.	Aver. Serum Cholest.	Aver. Lipid P	Ser. Chol.–Lipid P Molar Ratio
20–29					40	183	8.66	1.72
30–39	4	255	11.3	1.81	25	201	9.40	1.71
40–49	25	257	10.9	1.89	30	215	10.08	1.71
50–59	37	267	11.4	1.88	17	204	9.32	1.76
60–69	15	265	11.4	1.87				
70–79	1	240	10.4	1.85				
	82	263	11.2	1.885	112	198	9.3	1.72

TABLE 3.—*Individuals with Total Cholesterol Levels between 200 and 250 mg. per 100 cc.*

Age	Control			Coronary Disease		
	No.	Average Total Chol.	Average Molar Ratio	No.	Average Total Chol.	Average Molar Ratio
40–49	20	222	1.77	10	223	1.98
50–59	9	221	1.82	15	232	1.93

from 7.7 to 17.6 mg. per 100 cc. with a mean of 11.2 mg. per 100 cc. The difference between the mean of the normal subjects and the patients was 1.9 mg. per 100 cc. (fig. 2).

Serum cholesterol–lipid phosphorus molar ratios were computed for each individual. In the normal group the ratio fell between 1.30 and 2.09, with the mean of 1.72. In the coronary series the ratios fell between 1.52 and 2.43, with a mean of 1.88. Figure 3 reveals the difference in distribution of the molar ratios of the normal subjects and the patients with coronary arteriosclerosis.

The above results have been analyzed statistically and it has been found that the differences between the means of the serum cholesterol, serum lipid and the serum cholesterol-lipid phosphorus molar ratio of the patients with coronary arteriosclerosis and the control subjects are significant.

When the two groups are divided into age decades (table 2) it is seen that no significant difference in the average values for serum cholesterol, serum lipid phosphorus, or molar ratio is evident among the groups of the coronary series. However, in the control series a significant increase in the average serum cholesterol and average serum lipid phosphorus occurs in the age groups 30 to 39 and 40 to 49 years as compared with the 20 to 29 year group. This finding is in agreement with the recent report of Keys[9] who found increases in serum cholesterol with advancing years. There was no change in the molar ratios in the age groups 30 to 39 and 40 to 49, indicating that the increase in cholesterol in the normals was accompanied by a comparable increase in lipid phosphorus.

In table 3, the individuals in both groups with serum cholesterol levels falling between 200 and 250 mg. per 100 cc. have been compared. The average serum cholesterol and average molar ratios were computed. It can be seen that with fairly similar serum cholesterol levels the molar ratio for the coronary group is higher than the molar ratio in the control series. Thus in the patients with coronary artery disease with normal serum cholesterol levels, the molar ratio is frequently elevated.

Discussion

The above results confirm previous reports that the serum cholesterol levels of patients with coronary arteriosclerosis are generally higher than in control subjects. In addition, it has been shown that the average serum lipid phosphorus level tends to be higher in patients with coronary arteriosclerosis. However, the increase in lipid phosphorus is not proportional to the increase in serum cholesterol, resulting in an elevation of the serum cholesterol–lipid phosphorus molar ratio. Ahrens and Kunkel[10] have shown that the phospholipids are naturally occurring emulsifying agents which maintain the lipids of the serum in solution. If the serum cholesterol–lipid phosphorus molar ratio is elevated, there is, theoretically, an insufficient amount of lipid phosphorus to maintain all of the cholesterol in solution. It is possible that this abnormal state of cholesterol is one of the factors responsible for its deposition in the arteries, rather than the absolute level of serum cholesterol. Certainly there are many patients with arteriosclerosis in whom an elevation of serum cholesterol has not been recorded. Such was the case in 25 of the 82 patients with coronary arteriosclerosis in this series. Many of these individuals had elevated serum cholesterol–serum lipid phosphorus ratios with normal serum cholesterol values.

The average serum cholesterol level of 260 mg. per 100 cc. for the patients with coronary arteriosclerosis requires approximately 13 mg. per 100 cc. of lipid phosphorus to keep the molar ratio at the average level which has been found in healthy adults. However, the average lipid phosphorus for the group of patients with coronary arteriosclerosis was 11.2 mg. per 100 cc.

The serum lipid pattern of patients with coronary arteriosclerosis differs from normal in a number of respects in addition to the abnormalities in serum cholesterol and serum lipid phosphorus. In preliminary studies from our laboratory[11] it has been shown that the serum neutral fats and the total serum lipid are also elevated abnormally in patients with coronary arteriosclerosis. It is possible that these chem-

ical abnormalities are related to the findings by Gofman and his co-workers[12] who by physical means have demonstrated the presence of giant-size molecules in the serum in high concentrations in patients with coronary arteriosclerosis. Certainly for investigative purposes it will no longer be sufficient to determine a single lipid of the blood but rather it will be necessary to quantitate all of the lipid components. As more information becomes available it has become increasingly apparent that coronary arteriosclerosis is associated with complex abnormalities of the serum lipid pattern.

Conclusion

1. A group of individuals with proved coronary artery disease has been compared with a control group of apparently healthy adults with respect to certain lipid components of the serum. The following observations were made:

(a) The serum cholesterol and serum lipid phosphorus values were elevated in the patients with coronary arteriosclerosis as compared with the control group.

(b) The increase in serum lipid phosphorus was not proportional to the increase in serum cholesterol resulting in an increase in the serum cholesterol–lipid phosphorus molar ratio.

2. The possible significance of an abnormal serum cholesterol–serum lipid phosphorus molar ratio in the pathogenesis of arteriosclerosis has been pointed out.

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CLINICAL PROGRESS

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The Functional Importance of Coronary Collaterals

By CARL J. WIGGERS, M.D., SC.D.

THE PHYSICIAN attending a patient with a recent coronary occlusion is confronted with many questions of prognostic importance: How long will muscles in the ischemic area remain viable? What will determine the size, shape, and depth of the infarct? What are the chances that collateral blood supply will limit its extent, promote healing, and prevent subsequent aneurysmal dilatation? Are drugs likely to be helpful? Careful clinical observations followed by necropsy control can suggest answers to these questions; basic knowledge derived from experimental studies helps to establish the correctness of the answers.

ANATOMIC ASPECTS

The blood supply of mammalian hearts is derived from two coronary arteries arising from the root of the aorta. The left divides almost immediately into the left circumflex and the anterior descending rami. The former runs in the A-V groove to the left, reaches the posterior aspect of the left ventricle, and terminates in a posterior descending branch. The ramus descendens anterior circles left to the pulmonary artery and then runs downward in the interventricular groove toward the apex. Near its origin it gives off septal branches to the septum. The right coronary artery runs to the right in the A-V groove and terminates posteriorly in several descending branches on the right ventricle. Special twigs, variable in origin, supply the sinus nodal tissue. These are indicated in a composite drawing of figure 1.

Branches of the several main coronary arteries pass superficially in the general direction of the apex. They divide into intramural branches which course directly into the ventricular muscle. At the apex, coronary branches turn inward with muscle bundles to supply the inner layers of both ventricles and the papillary muscles. Anatomic studies have revealed that the branching of vessels within the myocardium is related to muscle bundles, but numerous intercommunications exist between vessels of different bundles.

In the dog's heart, the left atrium and ventricle are supplied largely by the two left coronaries, and the right ventricle by the right circumflex, but communications of arteriolar size or larger exist in superficial layers between territories supplied by the three principal coronary arteries. It should be noted that such collateral communications are apparently absent in the deeper layers.

In the human heart the distribution appears to be more variable. According to studies of Schlesinger, three general patterns of distribution can be recognized: (a) right coronary preponderance, (b) left coronary preponderance, and (c) a balanced distribution. However, Schlesinger and his associates were not able to demonstrate significant intercommunications between these systems in normal human hearts.

In addition to the aforementioned intercoronary communications, connections of intramural branches with the ventricular cavities

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and extracoronary vessels have also been demonstrated.

Hydraulic Principles

The demonstrations that anastomotic channels exist does not prove that they carry blood under normal or pathologic conditions. Flow of blood from one main vessel to tributaries of another through communicating channels requires a pressure difference, the magnitude of which depends on the resistance offered by the communicating tubes.

Let us examine the facts upon which predictions can be made of the probability that blood flow can be established through these various channels. During diastole the mean pressure in an occluded coronary artery is approximately 18 mm. higher than in the left ventricular cavity. Consequently, if any flow occurs it would therefore be *from* the coronary vessels *to* the ventricular chamber. During systole the mean pressure in the left ventricle exceeds that in an occluded coronary artery by about 45 mm., but the connections between the ventricular cavity and coronary arteries are compressed by myocardial contraction. It is therefore dynamically inconceivable that any material volume of blood could be transferred from the ventricular cavity even if communications of very large caliber were present. Experimental studies have corroborated such inferences: when the three principal coronary vessels are temporarily occluded, no blood flows from the peripheral ends of coronary vessels.

On the other hand, when a coronary artery is ligated, a mean pressure differential of approximately 66 mm. Hg exists between other branches of the aorta and the occluded vessel throughout the heart cycle. Since these communicating channels are not compressed during diastole, a flow during this phase would be dependent largely on the diameter, length, and number of such communications. It would also be determined by the duration of each diastole or, in other words, the heart rate. Since such collaterals are apparently developed better in hearts of dogs than in those of man, it may confidently be expected that the dog is a favorable animal for demonstrating their functional importance.

Experimental Evidence

For a number of years the present writer and his colleagues hopefully pursued experimental studies to demonstrate the existence of functional collaterals in the normal dog's heart, but without success. The most conclusive evidence that collateral flow is inadequate in the normal dog's heart was (a) the demonstration of Tennant and the writer that ligation of the main coronary artery causes the ischemic area to stretch rather than to shorten during systole, and (b) the further

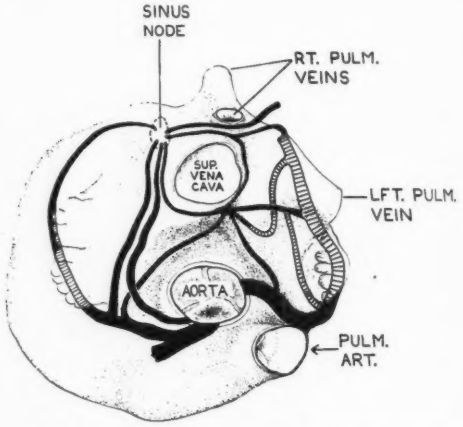


Fig. 1. Composite diagram illustrating the variable origins of arterial supply for the sinus node.

observation with Green that this cannot be prevented or abolished by drugs which elevate arterial pressure or have an alleged dilating effect on coronary vessels. Apparently, intercoronary communications are too small in relation to the pressure differentials which exist during diastole to transfer adequate quantities of blood. In short, in normal hearts of dogs the coronaries are functionally, though perhaps not anatomically, end arteries.

With this view the recent investigations of Prinzmetal and his group are apparently in disagreement. They maintain that collaterals of significant size exist in normal hearts of animals and man which serve a physiologically useful purpose. The evidence which they sub-

mit in favor of this view therefore deserves the most careful evaluation. The following serves as a brief summary of their various procedures and comments with respect to interpretations:

Procedure I. Human hearts obtained at necropsy were perfused through both coronaries with kerosene under equal pressures. Clamping of one coronary increased the flow through the other by approximately 4 per cent. Such results cannot be applied to the beating heart in situ, for the pressures used exceeded the differential pressures which can develop; the viscosity of the perfusion fluid was lower than that of the blood, and the vessels were neither compressed during systole nor under myocardial tension during diastole. Various types of experiments on the beating heart in situ in our laboratory have shown that clamping the right coronary artery has highly variable effects on left coronary flow, probably owing to alterations in cardiovascular dynamics. Also, although the flow of blood from the peripheral end of a severed coronary artery gradually increases after ligation of its main branch, it is never of sufficient magnitude conceivably to nourish the ischemic area.

Procedure II. When the left coronary artery was perfused with tiny glass spherules suspended in a radiopaque medium, those ranging between 70 and 180 microns apparently passed through vessels of arteriolar size to branches of the right coronary artery. Similarly, spherules 70 to 120 microns entered the ventricular cavities presumably through arterioluminal channels. Some beads of even larger size were recovered from the coronary sinus, suggesting the presence of arteriovenous shunts.

Since it is dynamically impossible for any consequential flow to be derived from the ventricular cavities in the beating heart, the passage of spherules of large size in the dead heart obviously does not furnish evidence as to sources of blood supply to a potentially infarcted region. It is also possible to overestimate the vascular caliber from the size of beads which pass. One can, for example, force marbles through an elastic rubber tube of much smaller diameter than that of the marbles themselves. Since the perfusion pressures used exceeded the possible differential pressures in the beating heart, and since the vessels might have become more expansile as a result of the incubation process which preceded injection, such a possibility cannot be excluded.

Procedure III. Human hearts similarly pretreated were perfused via a left coronary ramus with red cells rendered radioactive by incubation with P^{32}. A pressure of 100 mm. Hg was used for such perfusion. The ventricles were unrolled and placed on a flat surface, and the radioactivity of different regions was determined by a Geiger counter. The results apparently demonstrated that the epicardial regions of the right ventricle contain nearly as much radioactivity as the left ventricle.

Assuming that hemolysis and the postmortem diffusion of P^{32} from red cells were adequately controlled, the question as to a similar occurrence in the beating heart obviously required further investigation. The Los Angeles group were fully cognizant of this and therefore turned to the study of beating hearts.

Procedure IV. Radioactive erythrocytes were injected intravenously into moribund patients having coronary infarcts. Geiger counts of the hearts obtained post mortem revealed a high degree of radioactivity in the infarcted areas. These tests were supplemented by experiments on dogs: radioactive erythrocytes were similarly injected intravenously after ligation of the ramus descendens anterior. The heart was frozen rapidly and unrolled. Geiger counts and radioautographs again demonstrated nearly as marked radioactivity in the epicardial layers of the area supplied by the occluded ramus as in other regions of the ventricles, but the endocardial layers of this region exhibited significantly less radioactivity.

It is a common experience in research that experimental results which seem crucial at the moment turn out to be inadequate with aging. The apparently obvious conclusions regarding the efficiency of coronary collaterals which are suggested by these brilliant experiments must, however, be squared with other observations made at the same time. The Los Angeles investigators, as many others before them, noted that the ischemic area becomes cyanotic and that infarction generally follows in dogs which

survive. Hence the presence of radioactive red cells in an ischemic area could not have signified that the blood supply approached that of the normal myocardium.

The volume of blood found in a tissue after death is not a criterion of blood flow during life. It is extremely difficult to differentiate between blood in active circulation and that which may have stagnated, in the sense that the process of stagnation does not necessarily involve complete immobilization of corpuscles, but a slow onward displacement. Indeed, periodic expansion of an ischemic area alone might cause a slow forward movement of corpuscles. In such an event the rate of flow would necessarily be small, the oxygen consumption would be more complete (cyanosis), but the oxygen supply per minute would be wholly inadequate. Such a situation obviously explains the evidences cited in support of a different interpretation, namely that an active flow is demonstrated. Finally, Blumgart and his associates have recently pointed out the difficulty of being certain of "the amount of radiation contributed respectively by blood in surface veins, possible capillary extravasations incurred in infarction and rapid freezing, and the diffusibility of P^{32} from red cells into plasma even during short periods of time, particularly if hemolysis has occurred."

Summarizing, the distribution of radioactivity determined post mortem offers no crucial evidence for the existence of an adequate blood flow to a region deprived of its main coronary supply; whereas the cyanotic appearance is clear evidence of failure of a functionally useful blood flow.

Procedure V. Fluorescein injected intravenously in dogs after ligation of the ramus descendens was shown by the aid of cinematographic color photography to appear promptly in the margins of the involved area and to spread concentrically to its very center approximately in 16 seconds. Striking as such visual tests are, they give no information as to the magnitude of the collateral blood supply, or indeed as to whether spread of the highly diffusible dye occurred via blood vessels or lymphatic channels. It has been our experience that any dye similarly injected tends to remain localized permanently; it does not fade on recirculation of diluted dye. It was also noted by Prinzmetal and his group that the fluorescein coloration did not penetrate to the inner layers of the myocardium, but was limited to the outer third of the wall. This confirms the general opinion that collateral circulations such as exist are limited to superficial regions of the myocardium. Therefore, if their observations denote an adequate blood supply, it may be expected that the superficial layers of muscle will retain their viability at the time that the dye reaches this area. As already mentioned, myographic records of such surface fibers have demonstrated over and over again that, by the time the fluorescein was found to color the whole area (about 16 seconds), the muscle begins to stretch instead of shorten during systole. These composite observations would indicate that coloration of an area is not a good criterion of an adequate blood supply.

Procedure VI. The Los Angeles investigators, however, claim to have demonstrated by use of rapid motion pictures and measurement of ventricular borders in successive frames that bulging of the affected area may disappear or wax and wane; "the noncontractile myocardium regained its contractility a few seconds later." This was attributed to periodic variations in collateral blood supply. The present author and his many associates have recorded optical myograms following occlusion in hundreds of experiments and have never witnessed such a phenomenon, nor are such contractions reestablished after a coronary artery has been occluded for more than 20 to 60 minutes. It has been suggested elsewhere that these differing observations may be due to the fact that changes in the borders of the ventricles recorded cinematographically or otherwise represent composite effects of changes in position and volumes of the ventricles, and therefore cannot equal the accuracy of myograms which, when properly applied in the direction of surface fibers, accurately record the distance between two points.

Therefore, the results obtained by Prinzmetal and his group through employment of new and ingenious technics have not altered our opinion

that in normal dogs the collateral supply of the surface layers is not adequate to maintain contractions of sufficient force to prevent the ventricular wall from stretching in the affected region. As a corollary, it is highly improbable that any better functional supply could develop in human hearts which have demonstrably poorer collateral channels.

The Development of Collaterals

Abundant evidence exists that the potential intercoronary and extracoronary communications present in normal hearts can develop into functioning channels when a main branch is *slowly* occluded. The morphologic evidences are (1) that large intercoronary communications have been found post mortem in human hearts exhibiting sclerotic changes in one or more main branches, (2) that occasional instances have been reported in which complete occlusion of coronary arteries without infarction was seen, and (3) that pigs, which have no anatomically demonstrable vessels such as dogs, develop collaterals after chronic reduction in blood supply. The experimental evidence that intercoronary communications enlarge include the following observations: (4) When a main coronary branch is slowly occluded in dogs by mechanical clamps, cellophane bands, or osmotic devices, the retrograde flow from a peripheral end increases significantly over the normal, which is only a few drops per minute. The peripheral pressure also increases and the recorded pressure pulses may display earmarks of directly transmitted arterial pressures. (5) Temporary increase in aortic pressure in such preparations greatly accentuates such retrograde flow and pressure, whereas temporary clamping of other coronary arteries abruptly decreases or completely stops retrograde flow. (6) Myographic records taken from an area of slow occlusion in dogs which survive indicate that the region is undergoing shortening and that the newly developed collaterals are functioning in adequate fashion. Very occasionally—perhaps in animals which have developed sclerotic changes previous to ligation—this has also been found in chronic dogs that survive complete ligation. Such observations must be kept in mind in evaluating results of surgical procedures designed to revascularize the heart.

The interesting and hopeful clinical deduction may perhaps be drawn that progressive development of coronary sclerosis which primarily operates to throttle coronary flow may provide a natural mechanism leading to development of collaterals sufficient to mitigate or prevent infarction when a main vessel is subsequently occluded.

The factors which determine the development of such collaterals are not covered by the assertion that collateral circuits develop in ischemic regions owing to the need for more blood. The present writer has suggested that the slow establishment of differential pressure gradients following partial or complete occlusion of a main branch distends normally useless vessels to such a degree that they become pervious. This may be aided by their active dilation through development of a state of anoxia, which has been demonstrated to be the most powerful coronary vasodilator known.

The Effect of Drugs

It is naturally of clinical interest to inquire whether it may be anticipated that flow through collateral channels can be augmented by use of drugs demonstrated to have a vasodilator action. This includes the nitrites, xanthines, papaverine, and adenylic compounds. The nitrites should obviously not be administered in doses sufficient to reduce arterial pressure, particularly if this is already low. There is no substantial experimental evidence that alcohol, which is a potent dilator of cutaneous vessels, has a similar effect on the coronaries. In fact, the accumulation of blood in the skin may lead to a diminution in venous return and so reduce cardiac output and arterial pressures further. Coronary vasodilators might conceivably exert a favorable action (a) by increasing the caliber of potential communicating channels, (b) by reducing an alleged constriction of patent coronary vessels that supply the collaterals, or (c) by a passive dilation through elevation of arterial pressure in the event that marked hypotension exists.

The most critical experiments offer no support for the belief that any drug can penetrate connecting collaterals in normal hearts. None of the drugs investigated in our laboratory were able to abrogate or diminish the expansion of an ischemic area. Some observers, it is true, believe that the size of infarcts is reduced through their use; but such comparisons are necessarily made on different animals and must rely on measurements which do not include depth and are therefore hazardous owing to the variability of the infarcted area in dogs. Also in interpreting the effects of coronary vasodilators on surface infarctions a distinction should perhaps be made between effects due to opening of collaterals and those which are secondary to overlapping blood supplies. In dogs the margins of areas supplied by the three principal coronaries normally receive a dual blood supply. When a main coronary is constricted these margins naturally escape ischemia. By dilating the direct branches of the vessel which remains patent the blood supply may conceivably be somewhat extended.

The concept that intercoronary reflexes cause a constriction of other coronary vessels could not be confirmed in our laboratory and there appears to be no value in the use of drugs on such a basis. Pressor amines, such as epinephrine, norepinephrine, ephedrine, Neosynephrine, and others, have been advocated on the grounds that elevation of the pressure head plus dilatation of subsidiary coronary circuits should act favorably in forcing blood through collaterals. This is especially advocated in cases showing a low arterial pressure. Great circumspection should be used in the employment of such agents owing to certain counterindications. All of them increase the work of the heart, elevate pulmonary pressures, and tend to induce ventricular arrhythmias. In addition, epinephrine causes a deterioration of energy stores in cardiac muscle which would seem to be highly undesirable. Since the best experimental evidence indicates that the decline of arterial pressure following coronary occlusion is most probably due to failure of muscle which is still viable to compensate for the loss of contraction in ischemic areas, the use of cardiac stimulants, such as those of the digitalis series, would seem to be more plausible. Unfortunately, owing to the slow action of these agents, their effect on the caliber of coronary vessels has not yet been demonstrated satisfactorily in experimental animals.

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ABSTRACTS

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PHARMACOLOGY

Slotnik, I. L., and Teigland, J. D.: Cardiac Accidents following Vasopressin Injection (Pitressin ©). J.A.M.A. **146:** 1126 (July 21), 1951.

Although vasopressin injection (Pitressin) has been generally accepted as a safe medicament and used for the elimination of confusing gas shadows during cholecystography, extensive experimental work in the past has demonstrated profound cardiovascular effects resulting from its use. The most important of these is a decrease in coronary blood flow. It has been shown that acute myocardial degeneration can be produced in cats by administration of large doses of vasopressin. This effect could be produced only in old animals. The authors report two cases who were given 1 cc. of vasopressin injection during the course of cholecystography. One man, age 63, developed a typical myocardial infarction from which he subsequently recovered. Another man, age 54, died four and one-half hours after the injection, and autopsy showed old posterior wall infarction plus rheumatic mitral disease. Death was attributed to acute coronary insufficiency induced by vasopressin. The authors advise that the drug should be used with caution (if at all) in elderly patients.

KITCHELL

Frank, N., Strazza, J. A., Jr., and Helsper, J. T.: The Effects of Priscol (2 Benzyl-4, 5-imidazoline Hydrochloride) in the Treatment of Peripheral Vascular Diseases. Ann. Int. Med. **35:** 19 (July), 1951.

Twenty-two cases of peripheral vascular disease of various types were treated with Priscoline. The average daily oral dose was 200 to 250 mg. taken in divided doses. The highest oral daily dose was 500 mg. taken in divided doses. The average intravenous dose was 50 mg., given three to four times a day. The greatest intravenous dose was 240 mg., given in doses of 30 mg. every four hours. All patients exhibited increased collateral circulation as demonstrated by temperature studies. Intermittent claudication was abolished or improved in most patients. All patients claimed that their feet were warmer and that they felt much better than before treatment. In cases of thromboangiitis obliterans and frostbite all ulcerations healed. Contrary to expectations, fairly good results were obtained in the arteriosclerotic group. In the patients with thromboangiitis obliterans, good results were obtained with either large oral or relatively large intravenous doses. There were no alarming side reactions. Of two known cases of duodenal ulcer, one experienced epigastric pain controlled by antacids, while the other had no complaints. A third patient who gave no history suggestive of duodenal ulcer experienced anorexia, epigastric pain and nausea. A subsequent gastrointestinal series revealed an active duodenal ulcer. Symptoms were controlled by reducing the dosage of Priscoline and giving ulcer therapy.

WENDKOS

Brown, B. B., and Acheson, G. H.: The Influence of Procaine and Some Related Compounds upon Experimental Auricular Flutter in the Dog. J. Pharmacol. & Exper. Therap. **102:** 200 (July), 1951.

Studies on dogs in whom auricular flutter was

produced by the method of Rosenblueth and Garcia are reported. The rate of flutter was increased by stimulation of either the vagus or the sympathetic nerves. Diethylaminoethanal and diethylaminoethyl 2,4-dichlorobenzoate exhibited the same effects in innervated or denervated hearts, namely, a reduction of both auricular and ventricular rates and frequently abolition of the flutter. A similar effect was observed with procaine in the decentralized heart. In the intact heart, however, procaine exhibited a more marked auricular slowing, an acceleration of the ventricular rate and a decrease in the incidence of reversion to sinus rhythm. Procaine thus apparently blocks the effects of vagal stimulation upon auricular and ventricular rates.

SAGALL

Lu, F. C.: The Augmenting Effect of the Pressor Hormone of Pituitary Extract upon the Contraction of the Isolated Perfused Mammalian Heart: the Bearing of Coronary Flow on Heart Contraction. J. Pharmacol. & Exper. Therap. **102:** 145 (July), 1951.

In the perfused rabbit and dog heart the pressor hormone of pituitary extract results in an increased amplitude of cardiac contraction. This effect is due to constriction of coronary vessels rather than to a direct myocardial stimulation, for the same phenomenon may be produced by lowering the perfusion pressure, which decreases the coronary flow. The resulting augmentation of the amplitude of the heart beat in these experiments is not due to anoxia or the release of epinephrine or an epinephrine-like substance. The authors point out that the myocardial effects of many substances tested on the perfused heart may be due only to the constricting effect of the substance upon the coronary flow and not the result of any specific direct action upon the myocardium.

SAGALL

Kuhns, K.: Treatment of Ventricular Tachycardias. Ztschr. f. Kreislaufforsch. **40:** 415 (July), 1951.

Intravenous infusion of epinephrine in an amount of 10 μg. per kilogram per minute produces ventricular tachycardia of several minutes' duration in the anesthetized rabbit. This dose of epinephrine is necessary for the production of the arrhythmia. It remains unchanged in repeated experiments and may be considered as a threshold value. Premedication of rabbits with moderate doses of quinidine (2.5 mg. per kilogram daily for two weeks) increased this threshold to more than 31 μg. per kilogram per minute, while daily administration of toxic doses of quinidine (10 mg. per kilogram) increased the threshold only slightly. Premedication by Hydrergin for two weeks prevented the appearance of epinephrine-produced ventricular tachycardia or increased the threshold to more than 24 μg. per kilogram per minute. The effect of the latter drug is ascribed by the author to a direct depressing action on ectopic impulse formation in the ventricles in addition to alterations of the sympathetic-parasympathetic balance controlling the heart action.

PICK

Kreul, W., and Orth, O. S.: Treatment of the Hypotensive States of Spinal Analgesia with Dilute Neosynephrin Solution. Anesthesiology **12:** 455 (July), 1951.

The authors discuss the significant pharmacology of Neosynephrin and describe a technic for the administration of dilute Neosynephrin solution by continuous intravenous infusion in patients subjected to spinal anesthesia. By varying the rate of flow of the infusion the patient's blood pressure may easily be maintained within his usual range and the hypotensive states of spinal analgesia may be quickly treated. The possible complications of this method are enumerated and discussed.

SAGALL

Kensler, C. J., and Elsner, R. W.: Tetraethylammonium and Cholinesterase Activity. J. Pharmacol. & Exper. Therap. **102:** 196 (July), 1951.

Tetraethylammoniun is a weak inhibitor of human serum cholinesterase. When low concentrations of acetylcholine are employed it is a weak inhibitor of rat brain cholinesterase, whereas with high substrate concentrations it increases rat brain cholinesterase activity. The authors suggest that this latter effect is due to the prevention of inhibition caused by excess substrate.

SAGALL

Callaghan, J. C., and Bigelow, W. G.: An Electrical Artificial Pacemaker for Standstill of the Heart. Ann. Surg. **134:** 8 (July), 1951.

In experimental intracardiac surgery, general hypothermia has been induced as a means of lowering the oxygen requirements of the animal and thus lessening the demand on the circulation. At these low body temperatures cardiac standstill occurs rather frequently. An electrical apparatus was designed and constructed which could deliver stimuli that were similar to pulse pattern, pulse duration, pulse delay and frequency. These impulses were delivered to the area of the sinoauricular node either by an electrode applied externally to the area or by an electrode passed down the jugular and superior vena cava to the region of the sinoauricular node.

Dogs were cooled until their rectal temperatures fell below 21.9 C. At these temperatures cardiac standstill or marked slowing of the heart occurred. Then cardiac contractions were maintained by the artificial electrical pacemaker. The maximum rate that could be obtained in a heart that had completely stopped was similar to that of the slow rate of the hypothermia. Artificial heart action was maintained for as long as 70 minutes. Then the animal was

warmed to normal body temperature and spontaneous heart action resumed.

In animals at normal body temperature arrest of the heart was produced by right vagus nerve stimulation. During the period of standstill, artificial beats could be produced with the electrical pacemaker. When right vagal stimulation and the electrical pacemaker were used simultaneously, cardiac standstill did not occur. Furthermore, in animals at normal body temperature it was possible to vary the pulse rate from 60 to 200 per minute by stimuli from the artificial pacemaker.

It is felt that experimentally the heart action can be controlled satisfactorily by an electrical artificial pacemaker. This may be of value in intracardiac surgery, sudden cardiac arrest or resuscitation of persons suffering from exposure to extreme cold.

FROBESE

Baggenstoss, A. H., Schick, R. M., and Polley, H. F.: The Effect of Cortisone on the Lesions of Periarteritis Nodosa. Am. J. Path. **27:** 537 (July), 1951.

The writers report on two patients with periarteritis nodosa treated with cortisone. Following dramatic relief of fever and symptoms, both patients gradually developed cardiac and renal failure accompanied by electrolyte deficit. Death was caused by uremia in one case, by hypertension and myocardial infarction in the other. The histologic examination showed a remarkable healing of all arterial lesions in the first case, with the paradoxic end result of complete obliteration by intimal fibrosis of the small arteries in the heart, kidneys, liver and mesentery. Other organs were involved to a lesser degree. In the second case, a similar widespread arterial damage was noted accompanied, however, by small aneurysm and thrombus formations. In both cases, the acute arteritis demonstrated by biopsy had disappeared. Case 1 was complicated by the development of caseous pulmonary tuberculosis, and in both cases a previous surgical history of duodenal ulcer was recalled in the postmortem finding of multiple ulceration of the small intestine.

The writers are cognizant of previously reported spontaneous healing of the lesions of periarteritis nodosa but they comment on the speed with which healing occurred in their cases treated with cortisone.

GOULEY

Kay, J. H., and Blalock, A.: The Use of Calcium Chloride in the Treatment of Cardiac Arrest in Patients. Surg., Gynec. & Obst. **93:** 97 (July), 1951.

The authors report on the use of 2 to 4 cc. of 10 per cent calcium chloride in the treatment of impending ventricular standstill or of actual standstill occurring spontaneously or following the successful electrical defibrillation of a heart in ventricular fibrillation. The drug was injected into the left ventricular cavity in the case of four patients who were being operated upon for the correction of a congenital anomaly of the heart. In three of the patients the previous administration of 0.5 cc. of 1:1000 epinephrine hydrochloride had failed to restore a normal heart beat.

It was the opinion of the authors that calcium chloride is not necessarily superior to epinephrine hydrochloride, but that it should be considered an effective cardiac stimulant. Regardless of the drug used, vigorous cardiac massage should always be carried out until an effective beat is restored.

ABRAMSON

Payne, W. W., and Wilkinson, R. H.: Nephrotic Edema Treated with an Ion-Exchange Resin. Lancet **2:** 101 (July 21), 1951.

Six children with the nephrotic syndrome, when treated with a cation-exchange resin, showed reductions in body-weight and edema. The dangers of acidosis, a low serum potassium level, and a raised blood urea level are noted. Decreased or negative balances for sodium and potassium with increased fecal and decreased urinary output are shown.

BERNSTEIN

Pollak, O. J.: Effect of Bile Acids on Atherosclerosis Induced by Cholesterol Sols. Geriatrics **6:** 234 (July–August), 1951.

Intravascular injection of colloidal desoxycholic acid in rabbits results in intimal-subintimal damage to blood vessels which is comparable to the effect of similarly introduced hydrophobic colloids. Simultaneous intravenous injection of desoxycholic acid and cholesterol results in more severe vascular alterations than injection of either of the two substances alone.

Desoxycholic acid injection in rabbits results in dilatation of the portal vein and in periportal edema. Large doses of albumin injected intravascularly, together with desoxycholic acid, prevents the action of the bile acid on the portal system but fails to neutralize the effect of the bile acid on the blood vessels.

BERNSTEIN

PHYSIOLOGY

Aviado, D., Jr., Li, T. H., Kalow, W., Schmidt, C. F., Turnbull, G. L., Peskin, G. W., Hess, M. E., and Weiss, A. J.: Respiratory and Circulatory Reflexes from Perfused Heart and Pulmonary Circulation of Dog. Am. J. Physiol. **165:** 261 (May), 1951.

The hyperpnea of muscular exercise is arranged so that the increased oxygen requirement is met while arterial pCO_2 and pH are almost unchanged from control values. The authors point out that this hyperpnea is probably due to excitatory nervous influences impinging on the respiratory center. As a

result the center becomes as maximally active as is consistent with normal carbon dioxide tension and acidity. No such excitatory nervous influences of appropriate strength have been demonstrated during exercise. Previously demonstrated afferents from joints (active or passive movement) are active during exercise but are not intense enough to account for the whole hyperpnea. It is suggested that summation of a great number of discrete and diverse impulses, collectively large but individually small, may account for the hyperpnea. The present study deals with reflexes from lungs, heart, and intrathoracic blood vessels. Reflexes from lungs (von Bezold), expressed as respiratory depression or apnea followed by tachypnea, in response to veratrum alkaloids, were used to demonstrate reflex activity of an animal preparation. The only stimulating effects found were an increased rate of respiration when pulmonary venous pressure was elevated and after the apnea induced by veratridine. In these experiments rises in great vein and right atrial pressure did not stimulate respiration. Chemoreceptor effects upon respiration and circulation (except those due to veratridine) were absent from heart, lungs, and pulmonary vessels.

Circulatory reflexes arising in the right atrium (but not great veins) and proximal pulmonary artery produce bradycardia and vasodilation on raising pressure in these two areas. This is different from the results of Bainbridge and MacDowall, who used cats. Pulmonary receptors sensitive to veratrine and the pulmonary pressoreceptors appear to be in the pulmonary veins.

OPPENHEIMER

Feldberg, W.: The Physiology of Neuromuscular Transmission and Neuromuscular Block. Brit. M. J. 4713: 967 (May 5), 1951.

The author presents a comprehensive physiologic review of neuromuscular transmission and block in which evidence of the dependency of muscular contraction on acetylcholine is discussed. There is always some leakage of acetylcholine during the resting state of muscle, and this produces a miniature end plate potential which is subthreshold for excitation. He believes that the idea of a resting state at the nerve endings must be relinquished. When depression occurs in muscle, it is due either to the injection of large amounts of acetylcholine or to the frequent stimulation of eserinized muscle. In summary, he states that depolarization of the end plate by acetylcholine leads to propagated excitation followed by contraction. If the depolarization of the end plate spreads to the muscle fiber, depression or contracture results. Inasmuch as contracture is physiologic, the depression results in neuromuscular block such as is produced by Decamethonium. Normally excessive depression is prevented by a ferment in the nerve endings (cholinesterase). Three possible conditions leading to neuromuscular block are mentioned: (1) desensitivity of the end plate to the depolarizing effect of acetylcholine; (2) release of too much acetylcholine; (3) insufficient release of acetylcholine by the nerve impulse. Tubocurarine reduces the depolarizing influence of acetylcholine, decamethonium produces too much depolarization, and botulinus toxin is responsible for the inability of nerve endings to release acetylcholine.

The contracture function of small nerve fibers in the motor roots differs in the lower forms and in mammals, but it has been shown that mammalian function can ingeniously adapt the function of these lower forms in the development of postural reflexes.

TANDOWSKY

RHEUMATIC FEVER

Bustamante Riofrío, R., Kohout, F., and Schlesinger, P.: A Clinical Study and Statistical Analysis of 110 Cases of Mitral Stenosis. Arq. brasil. cardiol. **4:** 1 (March), 1951.

Among 923 patients with heart disease studied at the Moncorvo Filho Hospital in Rio de Janeiro, rheumatic fever was the third ranking etiologic factor, following hypertension and arteriosclerosis. Mitral stenosis, either as an isolated or associated valvular lesion, occurred in 110 cases, or 57.6 per cent of the total group with rheumatic cardiac disease. A rheumatic history was elicited in 81.9 per cent of this series, with a definite predominance of joint manifestations. There were 30 patients over 40 years of age, and it was noted that the clinical course of the disease seemed to be more benign in these cases, with a longer asymptomatic period following the diagnosis of the valvular lesion. The course of the disease was more severe in women than in the men, who, as a rule, had a more favorable outlook. Associated mitral and aortic disease which occurred in 18 patients seemed to be better tolerated and for a greater length of time than pure mitral stenosis, although they had a more rapid course after the onset of heart failure.

SCHLESINGER

Paddu, V.: Rheumatic Heart Disease with Normal Rhythm and Very Large "a" Waves in the Jugular Pulse. Am. Heart J. **41:** 708 (May), 1951.

The author presents clinical case reports of two living patients with chronic rheumatic mitral stenosis, and large venous pulsations limited to the base of the neck. In the lower part of the neck only, these pulsations consisted of large "a" waves in the phlebogram. The author believes that the big "a" waves are due to forceful systole of the right auricle against a stenotic tricuspid valve. In the presence of venous engorgement, a systolic pulsation is presumptive evidence of tricuspid involvement with incompetence, and a presystolic pulsation without venous engorgement is a presumptive sign of

dynamically pure tricuspid stenosis. The author is puzzled by the absence of hepatic pulsations in the patients studied. In an addendum, the author summarizes a recent report of Grishman and associates who studied 14 patients with presystolic liver pulsation in the absence of tricuspid stenosis. Some also showed a prominent "a" wave in the jugular tracing. These authors explain the strong presystolic pulsation as being due to resistance to right atrial outflow with reflux to the liver, caused by right heart failure, right ventricular hypertension, pericardial effusion, pulmonary hypertension and interatrial or aortic-atrial shunts.

HELLERSTEIN

Brown, T. McP., Wichelhausen, R. H., Merchant, W. R., and Robinson, C. B.: A Study of the Antigen-Antibody Mechanism in Rheumatic Diseases. Am. J. M. Sc. **221:** 618 (June), 1951.

The authors present the hypothesis that pleuropneumonia or L organisms may behave as antigenic agents in the pathogenesis of rheumatic diseases. This is based upon the finding of L organisms of the joints of man and animals, and upon the possibility that these forms may persist intracellularly. Inhibition of the L organism in vitro was demonstrated using various antibiotics of which Terramycin was the most effective; penicillin was relatively inactive. Clinical studies were conducted to evaluate the effects of antibiotic therapy on patients with rheumatic diseases. The results showed two types of responses: one group tolerated the drug well and was improved; the others experienced exacerbations of the disease which were attributed to the increased release of antigen by the antibiotics. Smaller doses were employed effectively in the latter group. Cortisone was described as able to block the exacerbation induced by antibiotics by inhibiting antigen-antibody reactions. Human serum albumin administered to eight patients with active rheumatoid arthritis produced clinical improvement for six to eight hours. The combination of albumin and antibiotic was used in several arthritics with good results. It is suggested that the L organisms are antigenic and may produce tissue hypersensitivity; this is increased by antibiotics which cause release of antigen and is blocked by Cortisone or human serum albumin.

SHUMAN

Hirsch, J. G., and Flett, D. M.: Acute Rheumatic Fever in the Young Adult White Male. Am. J. M. Sc. **221:** 599 (June), 1951.

The authors summarize the significant clinical findings in 109 cases of acute rheumatic fever occurring in air force personnel over a period of two years. In this group of patients, 78 per cent could recall an upper respiratory tract infection preceding the onset of the disease, with a mean time interval of 19 days between the respiratory symptoms and rheumatism. Migratory arthritis occurred in 94 per cent of the cases. Cardiac findings included mitral insufficiency in 15 patients, aortic insufficiency in 11 patients and mitral stenosis in two patients; mild cardiac decompensation occurred only twice. Sinus bradycardia was noted in 58 per cent of the patients during the course of their disease. Pericarditis was observed in 14 cases, of which only one presented electrocardiographic manifestations. Rheumatic pneumonitis was described in eight cases, while two others showed signs of peritonitis. Electrocardiographic abnormalities appeared in 88 per cent of the entire group. Laboratory studies showed evidence of streptococcal infection either by throat culture or by antistreptolysin titer in every patient except one. Comparison of a salicylate-treated group with a control group did not show any significant differences in the duration of the disease or the development of valvular heart disease.

SHUMAN

Taran, L. M., and Jablon, J. M.: Eight Years Experience with the Hemolytic Streptococcus, Group A, in a Rheumatic Colony of Children. Bull. St. Francis Sanatorium **8:** 1 (July), 1951.

Streptococcal bacteriologic and immunologic studies in a rheumatic colony of children aged 6 to 16 years are presented. The immunologic responses of the rheumatic patient to the nonspecific extracellular antigens of the hemolytic streptococcus such as the antistreptolysin O titer, the antistreptokinase titer and the antihyaluronidase titer do not present a pattern significant of rheumatic activity. Rheumatic fever patients do show a high degree of cutaneous sensitivity to the type-specific antigen M of the hemolytic streptococcus. Desensitization to the M fraction of all known types of hemolytic streptococci may be accomplished in a significant number of rheumatic patients by a slow process of "immunization." This type of "immunization" seems to have affected the general incidence of recurrences and reactivations in the rheumatic colony of children under observation though not enough studies have as yet been done to make them statistically significant.

BERNSTEIN

Kantor, H.: Childhood Emotional Patterns and Rheumatic Fever. Bull. St. Francis Sanatorium **8:** 32 (July), 1951.

Rheumatic fever is a disease presenting an etiologic problem which demands the attention of pediatrician, cardiologist, bacteriologist, immunologist and, of late, psychiatrist. It has been stressed that there is an intimate association of the psyche and the soma in rheumatic fever. The psyche is involved in the cardiac, vascular and choreiform expression of rheumatic disease. The psyche is also said to be associated with the allergic mechanism of etiologic significance in its pathogenesis.

Since rheumatic fever strikes at a time of delicate

emotional metamorphosis, it is particularly relevant that recognition and satisfaction of the basic emotional drives succeed. It is considered that rheumatic disease attacks an emotionally sick individual in whom psychologic tension has lowered the resistance of the host to the invading factor. Security and happiness in a child is essential for the prevention of rheumatic fever and its psychologic and cardiac complications. Psychotherapy in the treatment of active rheumatics is widely accepted. Whenever practicable, prophylactic psychotherapy against the onset or recrudescence of rheumatic fever is also recommended. The question is raised whether the severe personality difficulties of some rheumatic fever children really are an early choreiform expression of rheumatic disease or whether they exist in a nonrheumatic given the same emotional background. It is thought that perhaps all rheumatic children would have clinical chorea if their threshold to its clinical expression were lowered by psychologic tension.

BERNSTEIN

Spain, D. M., and Roth, D.: Effect of Cortisone and ACTH on the Histopathology of Rheumatic Carditis. Report of a Necropsied Case. Am. J. Med. **11**: 128 (July), 1951.

Cortisone and ACTH administered to a refractory case of acute rheumatic carditis produced little clinical significant response except a drop in the temperature and pulse rate during administration of cortisone. Necropsy also showed morphology no different from that of similar cases not receiving these drugs.

HARRIS

ROENTGENOLOGY

Di Chiro, G.: Mediastinal Tumor Simulating Left Ventricular Enlargement. Diagnosis by Means of Angiocardiography. Acta radiol. **35**: 299 (April), 1951.

The author describes a mediastinal tumor simulating massive left ventricular enlargement in a young boy. Angiocardiography was performed and indicated that the heart chambers were normal in size. At operation a flat multicystic mass was found to surround the left side of the pericardium. The microscopic diagnosis was cystic lymphangioma.

SCHWEDEL

Denstad, T.: Arteriography in Two Cases of Malignant Tumors (Melanoma and Neurinoma). Acta radiol. **35**: 309 (April), 1951.

The author applied the method of differing angioarchitectural appearances of tumor tissue whose arterial supply has been injected with radiopaque dye, to a case of metastatic melanoma, and to a malignant neurinoma lying above the right kidney. Their appearance was rather similar, and was characterized by the presence of numerous small blood vessels with an irregular course, some corkscrew like, evidently newly formed and abnormal. These findings were more prominent in the case of malignant melanoma.

SCHWEDEL

Ponsdomenech, E. R., and Nunez, V. B.: Heart Puncture in Man for Diodrast Visualization of the Ventricular Chambers and Great Arteries. I. Its Experimental and Anatomophysiological Bases and Technique. Am. Heart J. **41**: 643 (May), 1951.

The authors describe the technic of direct ventricular puncture in dogs and man. A 5½ inch trocar was inserted between the xiphoid process and the seventh left costal cartilage, and directed cephalad. Penetration into the ventricular cavities is usually preceded by extrasystolies as the trocar touches the ventricular wall. When the trocar was allowed to follow freely the movements of the heart, alterations of rhythm occurred. These disappeared when the trocar was put under control. Visualization of the ventricular cavities, of the aorta, and of the pulmonary arteries, as well as the coronary arteries, were obtained by the injection of Diodrast. This method is called "cardioangiography" since the films are taken from the heart toward the vessels. Direct ventricular pressure curves were obtained in 1 case. This technic was applied 45 times on 30 patients without mortality or untoward results.

HELLERSTEIN

Hanelin, J., and Eyler, W. R.: Pulmonary Artery Thrombosis: Roentgen Manifestations. Radiology **56**: 689 (May), 1951.

The authors describe the clinical, roentgenographic and postmortem findings in five cases of thrombosis involving the main pulmonary artery or its major branches. The points emphasized in the roentgen diagnosis were: alteration in hilar contours, changes in the vascular pattern in the lung fields, and right heart enlargement in long-standing cases. The authors also describe a single case of multiple thrombosis of the tertiary pulmonary arteries, with roentgen findings simulating occlusion of major pulmonary arteries.

Pulmonary infarction was present in four of the six cases. The authors consider that when the thrombus obstructs a major vessel the following changes ensue: dilatation proximal to the block, enlargement and alteration of the contour of the vessel at the level of the thrombus, and decrease in the caliber of vessels distal to the thrombus causing increased radiolucency in the corresponding area of the lung.

SCHWEDEL

Tierman, W. S., Eisaman, J. L., and Lloyd, J. T.: Pulmonary Artery Obstruction. Report of a case

with Angiocardio-cardiographic Demonstration. Radiology **56:** 876 (June), 1951.

The authors describe a case of pulmonary artery obstruction, probably secondary to tuberculosis, with atelectasis of the affected (left upper) lobe. The right hilus was normal, the left apparently small and retracted in an upward direction. On angiocardiography the left pulmonary artery ended abruptly distal to the bifurcation of the pulmonary artery trunk. The authors suggest that this was the site of an incomplete obstruction of the artery or a complete occlusion which had re-canalized. The right ventricle and atrium were not enlarged.

The electrocardiogram showed marked right axis deviation with inverted T waves and high R waves in leads 2, 3, and aV_F, findings compatible with the diagnosis of chronic cor pulmonale. The patient had no past history significant of cardiac or pulmonary symptoms.

SCHWEDEL

Marks, M. O., and Zimmerman, H. A.: The Roentgen and Differential Diagnosis of Chronic Cor Pulmonale. Am. J. Roentgenol. **66:** 9 (July), 1951.

The diagnosis of chronic cor pulmonale in this series was based on the pathologic demonstration of selective enlargement of the pulmonary conus and artery, with or without hypertrophy of the body of the right ventricle, in the presence of pulmonary emphysema or other appropriate pulmonary causes for such enlargement.

The roentgenologic features stressed were bulge of the pulmonary artery segment in the postero-anterior position; prominence of the pulmonary artery and right ventricular conus in the right anterior oblique position when the left atrium was not enlarged; enlargement of the right ventricle projecting anteriorly in rotation into the left anterior oblique position of 65 degrees or more, especially when the left ventricular segment was not enlarged; increased circular density of the bifurcation of the pulmonary trunk into its right and left pulmonary arteries, seen in both the right and left anterior oblique positions.

The following conditions simulating chronic cor pulmonale were described: atrial and ventricular septal complex, isolated pulmonic stenosis, idiopathic dilatation of the pulmonary artery, mitral stenosis, thyroid heart disease, heart failure, kyphoscoliosis, aneurysm of the pulmonary artery, Ayerza's disease, age and habitus.

SCHWEDEL

Sussman, M. L., and Brahms, S. A.: Interpretation of Normal Cardiovascular Angiograms. Am. J. Roentgenol. **66:** 29 (July), 1951.

The authors discuss some of the limitations of angiocardiography and relate these to anatomic variations, influence of intrathoracic pressures, variations in the concentration of dye within the right heart chambers due to laminar flow and reflux into the inferior vena cava, superimposition, phase of the cardiac cycle, and variations in the technical factors inherent in the roentgenographic apparatus. They stress that the diagnosis of reopacification is hazardous and suggest that error in angiocardiography is diminished when serial roentgenograms are obtained, and when oblique or lateral views are possible.

Clinical, roentgenological and pathologic observations should confirm each other to avert serious error. This calls for technical as well as clinical teamwork. In general, left to right intracardiac shunts are usually poorly visualized; in such instances more information may be derived from catheterization. Illustrations are offered of some of the common and other less frequent pitfalls.

SCHWEDEL

SURGERY IN HEART AND VASCULAR SYSTEM

Monod, O., Babou, G., Kateb, E., and Ghazi, S.: The Mobilization of the Arch of the Aorta in Order to Reach the Bifurcation of the Trachea. J. Thoracic Surg. **21:** 492 (May), 1951.

In order to reach the left main bronchus in preparation for removal of the left lung in a patient, the authors mobilized the arch of the aorta and temporarily retracted it inferiorly and to the left. In this manner the desired procedure was carried out with much less difficulty. When the aorta was released, it returned to its normal position in the chest.

ABRAMSON

Beattie, E. J., Jr., Cooke, F. N., Paul, J. S., and Orbison, J. A.: Coarctation of the Aorta at the Level of the Diaphragm Treated Successfully with a Preserved Human Blood Vessel Graft. J. Thoracic Surg. **21:** 506 (May), 1951.

The authors present a case of coarctation of the aorta, located at the level of the diaphragm, which was successfully treated with a vessel graft. The coarctation, which was approximately 6.5 cm. in length, was excised between Potts clamps and a preserved arterial graft of approximately the same size was sutured in place. The patient convalesced uneventfully.

ABRAMSON

Miller, H. H., Callow, A. D., Welch, C. S., and MacMahon, H. E.: The Fate of Arterial Grafts in Small Arteries. Surg., Gynec. & Obst. **92:** 581 (May), 1951.

The authors investigated the problem of the duration of patency of experimental arterial grafts of small arteries. Both fresh and preserved homografts as well as fresh autografts were implanted in the femoral arteries of 39 dogs, and observations

were then made on the efficacy of the procedure at various intervals up to as long as one year.

Thirty-four of the grafts were found to be patent as demonstrated by dissection and arteriography. The remaining four became completely occluded. Upon gross examination, all the successful autografts were found to be entirely similar, both in appearance and texture, to the adjoining artery into which they had been implanted. However, in the case of homografts, differences were discernible. These segments were slightly stiffer, less elastic and paler. Histologically they were found to have undergone necrosis of all layers, followed by a collagenous replacement of the media and a fibrocellular replacement of the intima. Nevertheless, the homograft provided a functioning vessel segment with a structurally sound wall and lining of living cells.

It was concluded that arterial grafts of all three types would be useful for bridging defects in cases of human arterial injury or for replacing segments of small but essential arteries sacrificed in extensive radical surgery.

ABRAMSON

Buhr, G.: Hemodynamic and Electrocardiographic Alterations following Surgery in Sodium Evipan Anesthesia. Ztschr. f. Kreislaufforsch. **40**: 257 (May), 1951.

The author reports alterations of the circulation and of the electrocardiogram observed in 21 patients shortly after gastric resection, performed in all cases with intravenous sodium Evipan anesthesia. The principal changes in cardiodynamics, which were analyzed according to the method of Broemser and Ranke were, an increase of pulse rate, of pulse velocity, of the elastic resistance and of the diastolic pressure; the pulse pressure, the stroke volume and the work of the heart were diminished. The electrocardiographic changes consisted in prolongation of the Q-T duration without corresponding prolongation of the distance between first and second heart sound (Hegglin's "energetic-dynamic insufficiency"). Calculation of the time of isometric contraction and of ejection revealed marked shortening of the latter, and only insignificant or no alteration of the former value. All these returned to preoperative normal values within five days and are ascribed by the author entirely to the effect of the anesthesia.

PICK

Blalock, A.: A Consideration of Some of the Problems in Cardiovascular Surgery. J. Thoracic Surg. **21**: 543 (June), 1951.

The author reviewed the various conditions affecting the cardiovascular system which are amenable to surgery. Among those in which this approach has accomplished good or excellent results are constrictive pericarditis, wounds of the heart, systemic arterial and arteriovenous fistulas, and such congenital lesions as patent ductus arteriosus, coarctation of the aorta, pulmonary stenosis, pulmonary arteriovenous fistula and anomalies of the aortic arch. Moderate improvement has occurred in the case of essential hypertension, transposition of the aorta and pulmonary artery and anomalies of venous return. In all other disorders either surgery appears of doubtful value or suitable methods for its application have not as yet been developed.

ABRAMSON

Gütgemann, A., Grosse-Brockhoff, F., and Kaiser, K.: Hypertension and Myocardial Insufficiency in Traumatic Fistula between Renal Artery and Inferior Vena Cava and Their Surgical Treatment. Ztschr. f. Kreislaufforsch. **40**: 321 (June), 1951.

The authors report the case of a 37 year old man with arteriovenous fistula between a renal artery and the inferior vena cava following a gun shot wound of the chest. The diagnosis was made clinically and verified at operation. Clinical signs suggesting the diagnosis were progressive heart failure, a thrill and a loud systolic murmur over the right upper abdomen and the right lower back. The blood pressure was 190/100 mm. Hg. Cardiac catheterization was performed, and a higher oxygen saturation was found in the right auricle (15.3 volumes per cent) than in the superior vena cava (11.3 volumes per cent). A retrograde pyelogram showed atrophic calices and impaired excretory function of the right kidney. At surgery, a large communication between the right renal artery and the inferior vena cava was found and ligated and the markedly atrophic right kidney was removed. Three months after the operation the blood pressure had dropped to 140/90.

The authors point out that, in contrast to usual findings in arteriovenous fistulas, the diastolic pressure in this case was elevated before and dropped after ligation of the communication. The hypertension and subsequent heart failure before surgery is ascribed to an increase of peripheral vascular resistance due to excretion of vasopressor substances by the ischemic right kidney.

PICK

Swan, H., and Morfit, H. M.: Arterial Homografts: III. Use of Preserved Grafts in the Treatment of Neoplastic Disease Involving Peripheral Arteries. Arch. Surg. **62**: 767 (June), 1951.

Since smaller arterial transplants were known to live and function in the experimental animal, the authors decided to give the concept a clinical trial. Three cases of sarcoma in the right femoral area, all with invasion of the femoral artery, had radical excision of the neoplasm. In one, the arterial defect was bridged with a vein graft which was successful. In the other two, arterial homografts were available from the "artery bank."

In one case, the artery graft survived and its function was checked by arteriography and found to

be good. In the other case, the soft tissue wound over the artery graft separated and the graft was exposed. Although the wound was closed immediately by a sliding graft of skin, the artery graft ruptured and profuse hemorrhage occurred. It was necessary to ligate the femoral artery and amputate the limb.

It is pointed out that the use of preserved arterial homografts in bridging defects in main peripheral arteries may increase the adequacy of resection of certain peripheral malignant neoplasms without resulting in radical amputation of the extremity. When the tumor invades the wall of the artery, it can be resected and a graft of similar size can be obtained from the bank and sutured in the gap.

FROBESE

VASCULAR DISEASE

Moore, H. D.: Deep Venous Valves in the Aetiology of Varicose Veins. Lancet **2**: 7 (July 7), 1951.

Using venography the author investigated the state of the deep venous valves in patients with varicosities. Those who did not have a history of deep thrombophlebitis were able to be divided into two groups on the basis of the state of their deep veins. In one the valves were normal, while in the other no valves could be seen in the deep veins which appeared increased in size.

None of the patients with varicosities who had had deep venous thrombosis demonstrated visible valves. On venography, some showed small irregular vessels, a response resulting from thrombosis and recanalization, while in others the vessels were larger than normal, giving the impression that they had dilated after an ilial thrombosis.

It was the opinion of the author that when symptoms are present in a patient with varicosities, these are due to abnormal deep veins, even though they had never been subjected to thrombosis. Therefore, in such individuals one would not expect ligation of the superficial veins to produce a cure, since the root of the problem, the abnormal deep veins, is not touched. He believes that only when the superficial veins alone are involved will improvement occur with such a procedure.

ABRAMSON

Salvesen, H. A., and Mastrander, F.: Arteriovenous Fistula of the Lung. Report of 4 Cases, Including an Acyanotic Case. Acta med. Scandinav. **139**: 167, 1951.

The typical clinical picture of arteriovenous fistula of the lung is said to consist of a history of cyanosis of long standing, shortness of breath, dizziness and sometimes syncope, while the physical examination discloses polycythemia, clubbed fingers, and a normal spleen and heart. Three cases showing the typical features are described and a fourth case is reported in which there was no cyanosis. The lack of cyanosis in this case was attributed to a relatively small shunt. In another case the blood flow through the chest was calculated to amount to more than 30 per cent of the total blood flow. In the single patient who was treated surgically, death occurred two and one-half years after operation and was attributed to a subarachnoid hemorrhage, possibly arising from hemangioma in the central nervous system.

ROSENBAUM

OTHER SUBJECTS

Shaffer, B., Jones, G. W., Scully, J. P., and Pillsbury, D. M.: Systemic Lupus Erythematosus. Some Cutaneous Manifestations Related to the Diffuse Collagenous Diseases. Am. J. M. Sc. **221**: 314 (March), 1951.

The authors describe the skin lesions encountered in three patients with systemic lupus erythematosus. In each of the cases, an effort is made to relate the cutaneous manifestations to similar lesions recognized in other diseases associated with diffuse collagenous or vascular pathology. Among the lesions presenting in these patients were: (a) erythematous, scaling patches on cheeks, nose, and ears; (b) deep-seated, papulonecrotic tuberculid-like lesions; (c) erythema nodosum; (d) acute, diffuse noninflammatory swelling of the extremities; (e) gangrene; (f) sulfonamide rash; and (g) Reynaud's phenomenon. These unusual cutaneous manifestations appearing in lupus erythematosus were reminiscent of the lesions encountered in periarteritis nodosa, dermatomyositis, scleroderma, anaphylactoid purpura, rheumatoid arthritis, and thromboangiitis obliterans. It is suggested that these diseases in which diffuse vascular reactivity is a fundamental pathologic feature may be related, and that the adrenal cortex may play a role in their pathogenesis.

SHUMAN

Friedman, M. M., Goodfriend, M. J., Berlin, P. F., and Goldstein, T.: Extracellular Fluid in Normal Pregnancy. Am. J. Obst. & Gynec. **61**: 609 (March), 1951.

An increase in the plasma volume and extracellular fluid volume during pregnancy has been demonstrated repeatedly. In this study, the "bromide space" was determined using a 10 per cent solution of sodium bromide for the calculation of the extracellular fluid. Among the subjects used for these measurements were 25 normal antepartum and 15 normal postpartum patients in whom there was no evidence of toxemia or water imbalance. The results were in close agreement with those obtained using other methods, such as thiocyanate space. The volume of extra-cellular fluid in normal pregnancy at term was found to be 11.3 liters per square meter of body surface or 28.8 per cent of body weight. The normal nonpregnant women showed a volume of 9.5 liters per square meter. In the series of measurements on postpartum women, the extracellular volume was 10.2 liters per square meter. The data

indicate that the estimation of extracellular fluid volume on the basis of surface area gives more constant results than that calculated on the basis of weight. Using surface area for their calculations, the authors state that pre-eclamptic patients have significant increases in extracellular fluid above those found in the normal pregnancy.

SHUMAN

Dawber, T. R., Meadors, G. F., and Moore, F. E., Jr.: Epidemiological Approaches to Heart Disease. The Framingham Study. Am. J. Pub. Health **41**: 279 (March), 1951.

The United States Public Health Service has planned an epidemiologic study of cardiovascular diseases in Framingham, Massachusetts, a city of 28,000 population. The problems involved in setting up the study may be divided into four groups; professional, administrative, organizational, and technical. The subjects selected for this study receive a complete history and physical examination together with an X-ray of the chest, electrocardiogram, electrokymographic tracing, and a number of laboratory studies including serum cholesterol, phospholipid and S_f 10–20 fractions. Six thousand people in the age group of 30 to 59 years have been selected. The subjects will be re-examined biennially and will be followed for about 20 years.

From this study it should be possible to test a number of hypotheses with respect to factors associated with the development of arteriosclerotic or hypertensive cardiovascular disease.

WAIFE

Lowman, E. W.: Muscle, Nerve, and Synovial Changes in Lupus Erythematosus. Ann. Rheumat. Dis. **10:** 16 (March), 1951.

Autopsy material from 15 patients with lupus erythematosus was studied histologically. The most prominent changes were muscle degeneration and involvement of the venous circulation consisting of three phases: edema, cellular reaction and sclerosis. These histologic alterations were identical with those observed in some active cases of rheumatoid arthritis. In only one instance of lupus did the changes in the muscle suggest fibrinoid degeneration.

ABRAMSON

Keefer, E. B. C., Andrus, W. D., Glenn, F., Humphreys, G. H., Lord, J. W., Murphy, W. B., and Touroff, A. S. W.: The Blood Vessel Bank. J. A. M. A. **145:** 893 (March 24), 1951.

The problems of establishing a blood vessel bank are fully discussed. It is important that autopsy permission for donor graft material must be cleared rapidly after the death of the donor. The material must be removed within six hours of death to be useful. The authors discuss preparation and storage of donor material by the nutrient medium method and the quick freezing method. Extrême care and caution must be exercised in the preparation and use of these grafts in order not to jeopardize a promising new field of surgery.

KITCHELL

Lee, S. L., Michael, S. R., and Vural, I. L.: The L. E. (Lupus Erythematosus) Cell. Clinical and Chemical Studies. Am. J. Med. **10:** 446 (April), 1951.

Investigation of 17 cases of acute disseminated lupus erythematosus disclosed the L. E. cell in the marrow and peripheral blood of all. This cell is a polymorphonuclear leukocyte containing a large, round, homogeneous inclusion body which is stained by basic dyes and is Feulgen-positive. The inclusion body of the L. E. cell is altered nuclear material derived from polymorphonuclear leukocytes and lymphocytes. This material contains partially depolymerized desoxyribose nucleic acid and is identical both optically and chemically with the "hematoxylin-staining body" of Klemperer. The L. E. cell may be found occasionally in other conditions, but it is considered to be specific in 96 per cent of cases for lupus erythematosus. Biochemical studies indicate the L. E. cell may be found in clotted blood and does not depend on the presence of an anticoagulant for its formation, but only on the amount of time outside the body. The factor responsible for the L. E. cell phenomenon is said to be contained in the gamma globulin fraction of the plasma. This factor produces a very powerful stimulus to phagocytosis which causes the leukocytes to ingest the altered nuclear material, thereby forming the typical L. E. cell.

HARRIS

Patten, B. M.: The First Heart Beats and the Beginning of the Embryonic Circulation. Am. Scient. **39:** 225 (April), 1951.

When studied by means of a special technic and motion pictures the first heart beat of the living chick embryo shows that the myogenic beat occurs before either a specialized muscle conduction mechanism or nerve regulation affects the heart action. The very first movements are local fibrillary contractions along the right margin of the ventricular region in the embryonic cardiac tube. These fibrillations coalesce to produce movement of the entire right side of the single ventricle. After similar movement of the left side the rhythmic contractions of the entire primitive ventricle developed a slow regular pulsation. During this time the atrium has begun to develop. It, in turn, begins to exhibit contractile activity at a higher rate than that of the ventricle. The circulation begins when the peristaltoid contractions initiated in the atrium gradually increase in power and rate. During this time the sinus venosus is still unformed. This sinus has a higher contraction rate than the atrium and as it is incorporated into the heart it speeds up the

rate and causes contraction waves to start further posteriorly. These changes occur before there is any histologic differentiation suggesting specialized conduction systems.

WAIFE

Holden, W. D., Murphy, J. A., and Portmann, A. F.: Scalenus Anticus Syndrome. Unusual Diagnostic and Therapeutic Aspects. Am. J. Surg. **81:** 411 (April), 1951.

The authors reviewed the findings observed in their series of 42 patients with scalenus anticus syndrome. In all instances neurologic signs or symptoms were present, while in approximately half the cases vascular findings were also noted. A consistent observation was tenderness on palpation of the belly of the scalenus anticus muscle.

The scalenus anticus syndrome was divided into an acute and a chronic stage. In the acute stage, generally a history of acute trauma could be elicited, the pain was severe and diffuse, and muscle spasm existed. A prompt response to conservative therapy generally occurred. The chronic stage was not necessarily associated with trauma, while localized paresthesias and atrophy were more common. Complete relief of symptoms in most instances was obtained only after a scalene tenotomy. The chronic stage of the disorder frequently followed repeated prolonged exertion involving the musculature of the neck and shoulder regions.

The tests which were found of value in making the diagnosis of scalenus anticus syndrome were local tenderness of the belly of the involved muscles, the relief of pain following the injection of procaine into them, and the Adson maneuver.

In the treatment of the condition, if the relief of pain was not satisfactory following the injection of procaine into the scalenus anticus muscle, the stellate ganglion was infiltrated. If relief of pain was now obtained, thoracic sympathectomy was performed at the same time that scalenotomy was done.

ABRAMSON

Luft, U. C., Clamann, H. G., and Opitz, E.: The Latency of Hypoxia on Exposure to Altitude Above 50,000 Feet. J. Aviation Med. **22:** 117 (April), 1951.

In rapid decompression to altitude above 52,000 feet breathing oxygen, using a parasite compartment attached to a large low pressure chamber by a valve system, it was shown that loss of consciousness can be avoided only if the total exposure time does not exceed five to six seconds. Longer exposures lead to unconsciousness after a latent period of 15 to 17 seconds regardless of the ambient pressure or arterial oxygen saturation prevailing at that time. Hypoxia of this type occurs without subjective or objective prodromal signs. This latency of hypoxia shifts the physiologic ceiling of the subject breathing oxygen to higher altitudes with increasing rate of climb.

BERNSTEIN

Bellet, S., Nadler, C. S., and Steiger, W. A.: The Circulation Time (Arm to Tongue Time) in Large Pericardial Effusions: An Aid in the Differential Diagnosis between Large Pericardial Effusion and Cardiac Dilatation. Ann. Int. Med. **34:** 856 (April), 1951.

Circulation time measurements, in 13 cases of massive pericardial effusion and in one case of adherent pericardium, were normal in 11 and slightly prolonged in three. These findings indicate that in any given case in which the cardiac silhouette is much enlarged, the circulation time can provide a means for differentiating between pericardial effusion and cardiac dilatation. The circulation time would be expected to be markedly prolonged if the increased size of the cardiac silhouette is due mainly to cardiac dilatation.

WENDKOS

Peirce, E. C., II: Percutaneous Arterial Catheterization in Dogs with Special Reference to Aortography. Ann. Surg. **133:** 544 (April), 1951.

The author describes a simple and rapid method of catheterizing the aorta in dogs in order to secure repeated x-ray records of aortic grafts. A polythene catheter is inserted into a 13 gage short bevel needle, and the tubing is flushed and filled with isotonic saline or saline plus heparin. The needle is then inserted into a femoral artery and the catheter tip is advanced to the desired level in the aorta. The needle is withdrawn, leaving the catheter in place. Diodrast is injected through the tube into the aorta for purposes of x-ray visualization.

ABRAMSON

Harrison, C. V.: Experimental Pulmonary Hypertension. J. Path. & Bact. **63:** 195 (April), 1951.

The author previously showed that repeated intravenous injections of minute fibrin clots into rabbits produced fibroelastic intimal thickening in the pulmonary arteries. He utilized the same method in a study of right ventricular hypertrophy in rabbits as a sequel to pulmonary embolism.

Three groups of 10 rabbits were used. Group I was subjected to small biweekly injections for 20 weeks. Some of this group died before the completion of this period, generally soon after an injection. The others were sacrificed. Group II, similarly treated, were allowed to recover for another period of 20 weeks and then were killed. The third group, used as controls, remained untreated.

The pulmonary arteries were injected with radiopaque mixture and studied by x-ray examination for embolism. The ventricles were dissected from each other and their relative weights recorded. In Group I, in which embolization was continuous

up to the time of death, significant hypertrophy of the right ventricle was evident. Roentgen study did not reveal obstruction or occlusion of any grossly observable vessel, an expected finding in view of the small size of the embolic particles. Group II showed little or no hypertrophy of the right ventricle although histologic study showed a considerable remaining fibroelastosis in the pulmonary vessels. The author concluded that embolism was a stimulant to pulmonary hypertension which provoked right ventricular hypertrophy and that when embolization ceased, both hypertension and right ventricular hypertrophy regressed completely. Vascular spasm appeared to be the direct link between these emboli and the cardiac lesion.

Harrison thus concludes that tiny emboli exert no mechanical effect, but rather cause spasm not only at the site of impact, but also in adjacent areas.

GOULEY

Garn, S. M., and Gertler, M. M.: Age and Sex Differences in the Serum Cholesterol of the Aleut. Canad. M. A. J. **64:** 338 (April), 1951.

The Aleuts are a genetically homogenous group of Eskimos living in the Aleutian Islands. Their diet is based on fish, while cholesterol containing foods are largely missing from the diet. At the time of this study the Aleuts diet was low in cholesterol but high in neutral fats and amino acids (a low-calorie high-protein diet). The mean adult serum cholesterol of 81 native Aleuts did not differ significantly from adult Americans. No significant sex difference in total cholesterol was noted. The cholesterol ester–total cholesterol ratio closely approximated that of Americans. Despite a common diet, four cases of hypercholesterolemia were encountered. The evidence suggests that endogenous mechanisms are responsible for the maintenance of the serum cholesterol.

WAIFE

Takahashi, S., and Shinozaki, T.: A Method to Take a Kymogram of the Heart Along the Perimeter of the Transsection. Tohoku J. Exper. Med. **54:** (April 25), 1951.

The authors arranged an x-ray tube, a rotation table, a lead slit and a film cassette for this method. The film moves just behind the stationary slit which is 1 mm. wide, and cut out horizontally in the lead plate. A lead wire is set across the slit where it is intersected by the plane, containing the tube-focus and the rotation axis of the rotation table. A patient is placed on the rotation table. By this means they then do discontinuous or continuous rotatokymography.

BERNSTEIN

Haserick, J. R.: Plasma L.E. Test in Systemic Lupus Erythematosus. J. A. M. A. **146:** 16 (May [illegible]), 1951.

The L.E. phenomenon (rosettes of clumped leukocytes and L.E. cells in the bone marrow of patients with systemic lupus erythematosus) is well known as a diagnostic test. Using the patient's own marrow is difficult because the patient is often extremely ill and the marrow is often hypoplastic (giving false negative results). The plasma L.E. test in which plasma of the suspect is mixed with the bone marrow cells from another person is quite accurate. Twenty-three patients who reacted in a positive manner to these tests in the Cleveland Clinic are reported. The authors conclude that the procedure is valuable diagnostically; it may correlate many unrelated conditions, and it continues positive longer than any other tests during remissions of lupus erythematosus. It prevents wrong diagnoses, such as epilepsy and/or syphilis. Negative tests may occur with abnormally low gammaglobulin in patients who have systemic lupus erythematosus. The test is not valuable in making a prognosis.

KITCHELL

Brown, M. G.: Acute Benign Pericarditis. New England J. Med. **244:** 666 (May 3), 1951.

The observations made in 13 patients with acute benign pericarditis are reported. Pain in the chest, a pericardial friction rub, changes in the RS-T segments and T waves in the electrocardiograms, rapid alterations in the cardiac size, and a benign ultimate outcome were the outstanding features of this series of cases. One patient had paroxysmal auricular flutter. Several patients developed pleural effusions, which were bilateral in two cases. All patients were followed for 18 months and six were followed for three years. Except for recurrent pericarditis in two of them, all had an asymptomatic course.

ROSENBAUM

Lee, S. L.: A Simple Test for L. E. Cells. Am. J. Clin. Path. **21:** 492 (May), 1951.

A new method for demonstrating the presence of Lupus erythematosus cells is presented. It is neither more nor less specific than other methods, but is simpler to perform and is more sensitive. It permits clean-cut distinction between bloods which show the L. E. phenomenon and those which do not.

Venous blood is permitted to clot in a clean, dry test tube. After standing at room temperature for about two hours, the clot is "fished" out with a wooden applicator and discarded. In the process, the clot is traumatized so that some blood escapes from it into the serum. The tube is then centrifuged at 1000 to 1500 rpm, the serum poured off and smears made of the sediment. The smears are stained with Jenner or Giemsa stains and examined under low power and then oil immersion.

Few white cells are found and these are at the periphery of the smear. The finding of clumping of polymorphonuclear leukocytes, "rosette" formation, and free homogeneous nuclear masses ("hematox-

ylin bodies") creates suspicion, but a positive result is not reported unless true L. E. cells are found. The search requires no more than five minutes in positive cases, where at least one L. E. cell has been found in the first 100 polymorphonuclear leukocytes counted.

The blood of 11 patients with acute disseminated lupus erythematosus was examined by this method on 39 occasions. In one case L. E. cells were not found by the clot method or any of the older methods, including a study of heparinized bone marrow. In the other cases the correlation was complete, and in all positive cases L. E. cells were far more frequently encountered by the clot method.

BEIZER

Arieff, A. J., Newman, L. B., and Fizzell, J. A.: Electromyography. I. A Portable Electromyograph for Clinical and Research Purposes. Arch. Phys. Med. **32**: 320 (May), 1951.

Electromyography is a branch of medical science which deals with the eliciting, indicating, recording and evaluating of voltages produced within skeletal muscle. This paper outlines some of the desiderata of a portable electromyograph which is suitable for clinical and research purposes. It also describes the electromyograph which was designed to meet these requirements. Among its unique features are the accurate built-in calibrator, the versatile sweep circuit, the provision for calibrating duration of sweep, the wide range of sensitivity, and the use of a 16 mm. motion picture camera for photographing and titling each oscillogram.

BERNSTEIN

Arieff, A. J., Newman, L. B., and Fizzell, J. A.: Electromyography. II. Sixteen Millimeter Motion Pictures and a Means of Titling for Continuous Oscillographic Recording in Electromyography. Arch. Phys. Med. **32**: 324 (May), 1951.

A standard 16 mm. motion picture camera, having the magazine-loading feature, has been adapted to the purpose of getting vast numbers of completely identified permanent records from the electromyograph previously described.

BERNSTEIN

Smith, L. M.: Apparent Cardiac Effects from Recent Infections. Connecticut M. J. **15**: 374 (May), 1951.

There are described numerous cases of respiratory and intestinal infections which have been marked by the complication of acute myocarditis. Among these cases have been a small number of patients who develop such precordial pain that they might be confused with ordinary cases of acute cornary occlusion without infection. It was noticed on the electrocardiograms in all cases that the characteristic findings consist of T-wave changes almost exclusively. Rarely one sees a minor S-T or QRS change. The T-wave changes are apt to be found in any lead and may consist of change in one or more leads. The T-wave changes develop quickly and reverse themselves just as quickly. From day to day the T-wave direction does not necessarily progress steadily upward or downward, but may vary up and down. The T waves tend to be pointed. The amplitude of all waves in V_2 and V_3 generally was large. The P waves are seen to be occasionally flattened or inverted. Autopsy material is not available in this series. Other authors describe the pathology of this acute myocarditis in detail. There are complete reports available with reference to subepicardial and myocardial hemorrhage, myocardial degeneration, and areas of myocardial inflammation, with polymorphonuclear leukocyte invasion.

BERNSTEIN

Schleicher, E. M.: Erythrocyte Aggregation Factor in the Plasma and Serum of Patients with Acute Lupus Erythematosus. Science **113**: 558 (May 11), 1951.

The author reports the presence of an erythrocyte aggregation factor which causes clumping of washed group O Rh-positive red cells in a mixture of egg white and fresh plasma and serum obtained from patients with acute lupus erythematosus. This phenomenon occurs following refrigeration for one-half hour. The factor is not destroyed by activating serum or plasma at 56 C for 30 minutes. Samples of plasma and serum containing this erythrocyte aggregation factor also produced a so-called L. E. cell phenomenon. Further study is being made to see whether the cold phenomenon producing erythrocyte aggregation and the so-called L. E. cell phenomenon are produced by the same factor.

WAIFE

Evans, W.: The Use of the Phonocardiograph in Clinical Medicine. The Lancet 260: 1083 (May 19), 1951.

It should never be the purpose of phonocardiography to bring to light heart sounds or murmurs which do not yield to auscultation; its function is to show where these lie in relation to the separate phases of the cardiac cycle, and their exact incidence in the different parts of systole and diastole. The clinician is helped to tell the various forms of triple heart rhythm, enlisting this sign to help significantly in diagnosis, and can more easily recognize clinically, an innocent heart murmur.

The phonocardiograph shows that there are only three kinds of triple rhythm and the first is the only important one, the other two having most weight in differential diagnosis: (1) from addition of third heart sound; (2) from audible auricular sound; (3) from added sound in late systole.

The innocence or otherwise of a murmur on pho-

nocardiographic grounds is decided from its place in the cardiac cycle.

When more is known of its interpretation, phonocardiography will come into common use, and it will have as its chief function the according of greater precision to the art of auscultation, and will render unnecessary other more elaborate tests which impose unwarranted discomfort on a sick patient.

BERNSTEIN

Rudnikoff, I.: Insulin and the Carotid Sinus. Ann. Int. Med. **34**: 1382 (June), 1951.

In 10 diabetics it was possible to demonstrate repeatedly that insulin can increase the effects resulting from carotid sinus stimulation. The hormone may affect the vagus center so that ordinary impulses from any part of the body to it can produce exaggerated responses. The carotid sinus receptors thus serve as a convenient way of influencing vagus mechanisms. The hypoglycemic effect of insulin was eliminated by using comparatively small doses of the hormone and by the administration of glucose whenever blood sugar level fell below 80 mg. In three of the cases, where both syncopal and cardioinhibitory effects were observed, atropine and its derivatives were used with insulin as part treatment and were effective in eliminating these symptoms. Withdrawal of the insulin in two patients yielded the same beneficial results. These experiments were repeated on several occasions and showed essentially the same responses.

WENDKOS

Jernstron, P.: Air Embolism during Peritoneoscopy. Am. J. Clin. Path. **21**: 573 (June), 1951.

This is the report of the first instance of fatal air embolism complicating peritoneoscopy. A 19 year old girl with hepatolendicular degeneration underwent peritoneoscopy to obtain a liver biopsy to confirm the diagnosis. After approximately one-third of the usual amount of air utilized to induce pneumoperitoneum, respirations ceased. Autopsy examination suggested that air entered a mesenteric vessel or the inferior vena cava, although a definite puncture of a blood vessel could not be found. A retroperitoneal hematoma precluded the demonstration of the precise site of bleeding. Air was found in the heart and the brain.

WAIFE

Frailing, J. M., and Owen, C. I.: Chylomicrons of Blood, A Resume of Literature and a Recommended Counting Procedure. Am. J. Clin. Path. **21**: 508 (June), 1951.

The presence of fine particles in chyle was noted as early as 1770. However, it was not until 1846 that similar particles were found in blood. In 1907 Neumann showed the connection of these tiny particles with the ingestion of fat. Since then a number of different laboratory technics have been devised to study these minute particles. They have been studied by darkfield microscopy, nephelometry, and by physicochemical means. The authors describe a modification of a method involving darkfield microscopy and direct count. The method is reported as being quick, accurate, and simple. Normal subjects showed a temporary rise in chylomicrons in the blood after the ingestion of fatty foods. However, a patient with thoracic duct obstruction did not exhibit this postprandial increase in chylomicrons.

WAIFE

Forbes, G. B., and Perley, A.: Estimation of Total Body Sodium by Isotopic Dilution. II. Studies on Infants and Children: An Example of a Constant Differential Growth Ratio. J. Clin. Investigation **30**: 566 (June), 1951.

Radioactive sodium (Na^{24}) was injected into 21 infants and children. The serum was analyzed for sodium and radioactive sodium from 18 to 24 hours later and the urine was collected during this interval. The total "exchangeable sodium" was highest in the young infant, averaging 70 mEq. per kilogram in the 3,300 Gm. newborn, and declining in a curvilinear manner with age until adult values are reached (approximately 42 mEq. per kilogram). Analysis of this and other data show that a straight line relationship exists when sodium content is plotted against body weight on a double logarithmic grid.

Total sodium changes with body weight in a predictable systematic fashion, as a fractional power of body weight, and behaves as a constant differential growth ratio.

WAIFE

Gamble, J. E., and Patton, H. D.: Pulmonary Edema and Hemorrhage Induced by Hypothalamic Lesions in Rats. Science **113**: 626 (June 1), 1951.

Hypothalamic lesions were produced in anesthetized rats by a stereotaxic instrument. Acute pulmonary edema developed in 18 rats less than 24 hours after placement of these lesions. Severe hemorrhage and edema was found, with alveoli distended by fibrous transudate and often erythrocytes. Calculations reveal that only the accumulation of a dilute transudate such as plasma could account for the increased percentage of lung fluid.

In another group of animals which showed pulmonary pathology when sacrificed 24 hours postoperatively, there was a spotty distribution of hemorrhagic lesions. It was found that hyperthermia was not essential to the development of pulmonary edema and hemorrhage following hypothalamic lesions. Identification of the destroyed region revealed that there was bilateral damage just overlying the anterior half of the optic chiasm in most of these edematous animals.

WAIFE

Wolff, L.: Diagnostic Implications of Pericardial, Pleural and Pulmonary Involvement in Cardiovascular Disease. New England J. Med. **244:** 965 (June 28), 1951.

The clinical manifestations of acute myocardial infarction, acute idiopathic pericarditis, pulmonary embolism and dissecting aneurysm of the aorta are often quite similar, and the differential diagnosis in many cases is very difficult. The author emphasizes the diagnostic importance of pericardial, pleural and pulmonary involvement in these conditions and presents illustrative cases. In acute myocardial infarction pericardial involvement is noted one to several days after the onset of the attack and almost never after the first week. The signs are transitory and pericardial effusion is rare. In dicumarol-treated patients persistence of pericardial signs or their development after a week should suggest hemorrhagic pericarditis secondary to hypoprothrombinemia. Pleural involvement is not found in uncomplicated cases, but abnormal pulmonary signs, especially at the left base, are common. The pericardial involvement in acute idiopathic pericarditis is distinguished by its appearance at the onset of chest pain and its persistence for days or weeks. Pericardial effusion is uncommon or small in amount. Pleural friction rubs, progressive thickening of the pleura, or pleural effusion is almost invariably found and the involvement may be bilateral. Pulmonary signs when present are due to pulmonary compression consequent to pleural or pericardial effusion or to pulmonary infection. In pulmonary embolism a sound resembling a friction rub may be heard in the pulmonic area, but pericardial involvement does not occur. Pleural involvement is manifested by pleuritic pain, pleural friction rub or pleural effusion. Pulmonary signs may be found anywhere in the lung fields, but more commonly appear at the right base. Large pericardial and pleural hemorrhagic effusions may occur in dissecting aneurysm of the aorta and may be noted with or some time after the onset of pain. They may be persistent or recurrent. Pulmonary signs and findings are common.

SAGALL

Barbato, E., Pinto Lima, F., Cotrim, E., Merlino, G., and Moraes Dantas, O.: Some Aspects of the Pulmonary Artery in Schistosomiasis. Importance in Differential Diagnosis with Congenital Heart Disease. Arq. brasil. cardiol. **4:** 233 (June), 1951.

In a number of cases of schistosomiasis, the authors have observed roentgenologic evidence of a prominent pulmonary artery and conus segment, particularly enlarged in two patients. Both cases are reported, with special emphasis on the differential diagnosis with certain types of congenital heart disease. On the basis of angiocardiographic studies and cardiac catheterization, no evidence of congenital cardiac malformations could be demonstrated, thus leading to the diagnosis of pulmonary hypertension due to obliterative arteritis caused by *Schistosoma mansoni*.

The need for a more careful consideration of this diagnosis is pointed out, particularly in those areas where this disease is known to occur, since it may simulate a number of acquired and congenital cardiac conditions.

SCHLESINGER

Simkins, S.: Boeck's Sarcoid with Complete Heart Block Mimicking Carotid Sinus Syncope. J.A.M.A. **146:** 794 (June 30), 1951.

Only 66 autopsied cases of Boeck's sarcoid have been recorded in the literature and of these only 15 cases presented direct cardiac involvement. The author presents an unusual case with a 15-year history of carotid sinus syncope, the patient suffering from infrequent attacks of fainting in which the pulse rate became slow. Pressure over the right carotid sinus brought on syncope. In her last attack she suddenly developed weakness, dyspnea, and dizziness with a varying pulse rate. Electrocardiographic tracing showed complete auriculoventricular block with a ventricular rate of 44, ventricular extrasystoles and left bundle branch block. Five days later an electrocardiogram showed a cardiac rate of 79 and with minor grade of auriculoventricular block and a right bundle branch block. Six days later the electrocardiogram had reverted to the picture first seen. The patient died 13 days after the attack. Autopsy disclosed generalized sarcoidosis with massive involvement of the myocardium, partial involvement of the auriculoventricular bundle. The possible linkage of the sarcoidosis in this case with a 15 year history of carotid sinus syncope is discussed.

KITCHELL

Rosenow, O. F. and Cross, C. J.: Acute Benign Pericarditis. Arch. Int. Med. **87:** 795 (June), 1951.

Four cases of benign pericarditis are presented, of which three serve to present common variations of the disease. A known infection of the respiratory tract preceded the subjective onset of pericarditis in two cases. The admission diagnosis was "acute myocardial infarction" in two cases, "acute cholecystitis" in one and "acute pleurisy" in the last. The diagnosis of acute benign pericarditis was suggested shortly after admission, because all four patients showed the characteristic symptoms and signs as previously described. The diagnosis was confirmed by the alterations in the electrocardiographic pattern. The results of laboratory tests were contributory, but not entirely diagnostic.

Treatment with Aureomycin and Terramycin effected a rapid symptomatic improvement. However, the changes in the electrocardiographic pattern and the sedimentation rate did not revert to

normal any sooner than in the control cases. Three patients showed complete recovery in follow-up studies. The remaining patient has not been followed long enough to permit a conclusion in regard to complete recovery.

Unless one follows the clinical picture closely, in conjunction with repeated tracings from limb, unipolar and multiple precordial leads, acute benign pericarditis will continue to be mistaken for myocardial infarction.

BERNSTEIN

Forbes, G. B., and Perley, A.: Estimation of Total Body Sodium by Isotopic Dilution. I. Studies on Young Adults. J. Clin. Investigation **30:** 558 (June), 1951.

Radioactive sodium was injected intravenously into 32 healthy young adults. Measurements of total "exchangeable sodium" by the isotopic dilution method revealed an average value of 41.9 mEq. and 39.9 mEq. per kilogram of body weight for males and females respectively. The range for males was 32 to 54, and for females 36 to 42 mEq. per kilogram of body weight. During the 18 to 24 hour equilibration period only about 40 per cent of bone sodium exchanged with Na^{24}. From various studies, it was concluded that about 82 per cent of the total body sodium was measured by this method. The isotopic dilution method measures the portion of total body sodium which is intimately concerned with body fluid exchanges.

WAIFE

Caton, W. L., Roby, C. C., Reid, D. E., Caswell, R., Maletskos, C. J., Fluharty, R. G., and Gibson, J. G., III: The Circulating Red Cell Volume and Body Hematocrit in Normal Pregnancy and Puerperium. Am. J. Obst. & Gynec. **61:** 1207 (June), 1951.

Direct measurements of the circulating red cell mass during normal pregnancy and puerperium were made in 12 patients using the radioactive iron, tagged red cell technic. Following the injection of the tagged cells, 15 minutes were allowed for complete mixing in the pregnant patients before sampling. Plasma volume and extravascular thiocyanate space studies were also performed at the same time. From 6 to 12 determinations were made on each patient at five to six week intervals throughout pregnancy. During the puerperium, studies were conducted at the end of one week and between the twenty-fifth and sixty-sixth days.

The results showed an increase of 495 cc. of red blood cells with an increase of whole blood by approximately 1800 cc. The maximum blood volume occurs 60 days before delivery but may vary from 68 to 5 days prior to delivery. The iron demand for new hemoglobin formation was approximately 500 mg. in this group, and was satisfied by a normal unsupplemented diet. These demands were apparently satisfied by increased absorption and reutilization of iron by the bone marrow.

At the end of the first puerperal week, the red cell volume remains increased but the total blood volume delines rapidly as a result of a reduction of plasma volume. The red cell mass returns to normal by the second month after delivery.

The body hematocrit, representing the ratio of the plasma volume to the red cell mass, was compared to the large vessel hematocrit. Here it was found that the latter value decreased by 15 per cent as pregnancy progressed while the body hematocrit fell only 8.4 per cent. It was observed that the ratio of body to venous hematocrit increased during pregnancy which suggests that the greater part of new blood volume is accommodated by the larger transport vessels rather than being equally distributed between these vessels and the capillary bed.

SHUMAN

Gillanders, A. D.: Nutritional Heart Disease. Brit. Heart J. **13:** 177, 1951.

The author describes a form of heart disease thought to be due to malnutrition and invariably associated with progressive liver disease known to be caused by malnutrition. His series consists of 30 cases, 22 men and 8 women, aged 30 to 63 yrs.

The diet was composed of white bread, tea, sugar and porridge made from maize. The duration of symptoms was brief. Dyspnea was present in all but three. Twelve had a dry cough and 16 pain in the right upper quadrant. Generalized massive edema spreading from below upward and engorgement of the neck veins were present. Liver enlargement was present in all.

The heart was enlarged in all. There was a feeble apical impulse and pulsations, as seen fluoroscopically, were minimal. Sinus rhythm and a diastolic gallop were present. The most constant electrocardiographic abnormality seen in 12 of 20 tracings was a pattern of subepicardial injury.

Digitalis, digitalis and mercurials, aneurin, Brewers' yeast, alpha-tocopherol and testosterone propionate were ineffective. A well balanced diet within two to three weeks produced complete recovery in 13 and eight died. The hearts show hypertrophy of the walls of both ventricles and microscopically interfibrillary edema of the myocardium.

SOLOFF

Sattler, T. H., Marquardt, G. H., and Cummins, G. M.: Alkalosis Due to Hyperventilation. J.A.M.A. **146:** 1125 (July 21), 1951.

Hyperventilation may be severe enough to overcome the compensatory mechanisms and the pH of the blood then rises above the accepted upper limit of normal (7.45). The authors feel that respiratory alkalosis is an easily produced and often overlooked syndrome. Patients who have a slight, asympto-

matic, pre-existing alkalosis from other causes such as vomiting or excessive alkaline therapy, need only moderate hyperventilation to precipitate severe symptoms. The authors present three cases. Diagnosis was made by securing an initial venous blood pH determination, then having the patient hyperventilate to produce symptoms and repeating the venous blood pH determination. Venous blood pH determinations were made on a standard Coleman pH meter which gives readings 10 to 20 seconds after the needle punctures the vein and usually within 20 to 40 seconds after application of the tourniquet. The ease and rapidity with which this test can be made makes it a most valuable clinical aid in the correct interpretation of acid-base disturbances.

KITCHELL

Lippman, R. W.: Cation Exchange Resin in Treatment of the Nephrotic Syndrome. Arch. Int. Med. **88:** 9 (July), 1951.

An excellent diuresis was obtained on 11 of 14 patients by the use of cation exchange resins. Most of the patients who responded to resin administration have been maintained virtually free of edema for periods that vary up to one year. For several patients the difference in their clinical condition since the initiation of resin therapy is comparable to the dramatic effects produced by cortisone administration in a patient with severe rheumatoid arthritis. For example, one patient, who was bedridden for 18 months with profound anasarca, after a complete diuresis has returned to his former occupation with no disability, although he continues to show the blood and urinary changes characteristic of continuing glomerular nephritis.

Of the three patients who did not have diuresis, two were unable to take the resin in adequate amounts. Of the latter, one was a child. The other was uremic, with nausea and vomiting. The remaining patient apparently took adequate doses of the resin for a sufficient time, but no diuresis occurred.

BERNSTEIN

Nelson, W. P., Rosenbaum, J. D., and Strauss, M. D.: Hyponatremia in Hepatic Cirrhosis following Paracentesis. J. Clin. Investigation **30:** 738 (July), 1951.

Paracentesis was performed on two patients with hepatic cirrhosis. A clinical picture of apathy, weakness, confusion, anorexia, muscle cramps, hypotension, tachycardia, and hemoconcentration followed. The serum nonprotein nitrogen was elevated and hyponatremia was found. Hypertonic saline caused all these symptoms to disappear. Both patients developed symptoms concomitant with the decline in serum sodium concentration following paracentesis. This occurred despite the presence of an abnormally large total volume of extracellular fluid with an excessive total body sodium content. With a large amount of ascitic fluid in the peritoneal cavity, it appears that the extraperitoneal extracellular fluid (the effective fluid volume) was actually decreased in both patients when the hyponatremic syndrome developed, and it is likely the administration of hypertonic saline served to correct both the hypotonicity and the diminished plasma volume.

WAIFE

Yallow, R. S., and Verson, S. A.: The Use of K^{42}-tagged Erythrocytes in Blood Volume Determinations. Science **114:** 14 (July 6), 1951.

This paper describes experiments in which comparison studies of erythrocytes labeled with K^{42} and P^{32} were made. Radiopotassium has a short physical half-life of 12.4 hours, and emits beta and gamma particles which can be easily detected. The biologic half-life of the K^{42}-labeled cells in vivo ranged from 28 to 35 hours. Essentially the same values were obtained as with P^{32} in six instances of almost simultaneous blood volume determinations by the two methods.

WAIFE

Magida, M. G.: Epidemic Parotitis Complicated by Pericarditis and Serositis. Ann. Int. Med. **35:** 218 (July), 1951.

A 29 year old white male was first seen eight days after the sudden onset of left parotid swelling, subsequently proved by immunologic studies to have been the result of a mumps virus infection. His left parotid gland and left testicle were swollen and tender, and his oral temperature was 102.6 F. At that time, although he complained of a dull ache in the left lower anterior chest, a chest x-ray film as well as examination of the heart revealed no abnormalities. On the following day the chest pain became worse and physical examination disclosed the presence of a pericardial friction rub. An electrocardiogram made at that time was abnormal, the T waves being inverted in the limb leads and in the single precordial lead. The friction rub did not persist although electrocardiographic abnormalities were present for approximately 10 weeks. Disturbances of A-V conduction did not develop. Convalescence was relatively uneventful except for the occurrence of a complicating arthritis which subsided completely within a few weeks. Antistreptolysin titers remained normal throughout the entire illness, and at the time of his discharge from the hospital no residual evidences of a cardiac lesion could be detected by physical, electrocardiographic or fluoroscopic examinations. It is therefore concluded that, in this case, the involvement of the pericardium and synovial membranes of the affected joints represents an instance of serositis complicating the course of epidemic parotitis.

WENDKOS

Evans, J. P., Espey, F. F., Kristoff, F. V., Kimbell, L. D., and Ryder H. W.: Experimental and Clinical Observations on Rising Intracranial Pressure Arch. Surg. **63**:107 (July), 1951.

The authors tested the widely accepted concept that the clinical state produced by expanding intracranial lesions is characterized by an increase in intracranial and arterial pressures and a bradycardia. In the case of rhesus monkeys, only when the intracranial pressure was increased to a level which approached arterial pressure were these signs apparent. Moreover, they were not present in human subjects with artificially elevated intracranial pressures as high as or higher than those usually found with intracranial neoplasms.

It was concluded that reflex dilatation of cerebral arterioles rather than an increase in blood pressure is the usual mechanism whereby the cerebral blood flow is adjusted to an elevation of intracranial pressure. Therefore the use of such signs as a rise in blood pressure and a fall in pulse rate as an indication of a high intracranial pressure is not warranted, since they will be initiated only at much higher levels of intracranial pressure than occur even in fatal cases of acute intracranial hemorrhage or neoplasm.

ABRAMSON

Bollman, J. L., Fazio, A. N., and Faulconer, A., Jr.: Some Factors Influencing the Effects of Anoxic Anoxia. Anesthesiology **12**: 420 (July), 1951.

The authors studied the effect of several factors on the ability of white rats to withstand the acute effect of exposure to an atmosphere of reduced oxygen content. The resistance of the adult rat to the effect of anoxia was lowered by hypoglycemia (insulin), hyperthyroidism (thyroxine) and anemia (hemorrhagic), was raised by hypothyroidism (thiouracil), and was unaffected by hyperglycemia (glucose injection). Newborn rats were more resistant to the effects of oxygen deprivation than adult rats. Animals suffering a two-hour exposure to atmospheres containing 4.5 to 6.0 per cent oxygen were normal after a few days but did show some loss of appetite and required about twice as long to regain their pre-experimental body weight as did rats exposed to 20 per cent oxygen.

SAGALL

Gulotta, G. A.: Precordial Pain and Aortic Insufficiency. Bull. St. Francis Sanatorium 8: 46 (July), 1951.

The triad of symptoms, namely, precordial pain, a rise in blood pressure and tachycardia, has been observed for many years in children suffering from protracted rheumatic carditis and aortic disease. The implication has always been that precordial pain associated with aortic insufficiency might be explained on the basis of a decreased coronary filling resulting from a low aortic pressure. This reasoning falls short in explaining why many patients with a low diastolic pressure do not present this symptom complex. Further, it does not explain the paroxysmal nature of these attacks. The incidence of precordial pain in aortic insufficiency is greater in patients with a moderate reduction in diastolic pressure than those with an extremely low diastolic pressure. In addition, the minute coronary flow is actually increased because of the better filling during systole. By direct catheterization of the coronary sinus in cases of aortic insufficiency, it was demonstrated that the oxygen consumption in these cases is actually increased rather than decreased. It would follow then that the symptom complex of precordial pain associated with aortic insufficiency could not be explained solely on the basis of a decrease in coronary flow.

It is tempting to postulate the following explanation for the cause of paroxysmal attacks in these patients. If the assumption is correct that in aortic insufficiency the minute coronary flow is increased, but relatively fixed, one might assume that the following train of events may possibly occur in patients having these paroxysmal attacks. A psychic stimulation produces a reflex tachycardia. The increase in cardiac rate also increases cardiac work. An increase in cardiac work presupposes an increase in oxygen consumption by the heart muscle. Since the coronary flow is fixed, the myocardium does not receive the supply of oxygen required under stress. This causes a relative myocardial ischemia with resultant pain. The pain produces further psychic stimulation for the propagation of this train of events.

BERNSTEIN

Mukherjee, S. R., Calcutta, M. S., and Rowlands, S.: A Direct Method of Measuring the Circulating Blood Volume. Lancet **2**: 98 (July 21), 1951.

A direct method for measuring circulating blood volume by using red blood cells labeled with radiophosphorus is described. The sources of error are discussed, and the over-all error of the method has been checked by measurements in vitro. The circulating blood volume has been measured in 21 dogs, with an average of 9.5 $\pm$ 1.7 ml. per 100 Gm. of body weight. The clinical possibilities of the method are discussed. With modification the method could give a reliable estimate of blood volume within 30 minutes of injection.

BERNSTEIN

BOOK REVIEWS

The Kidney. Medical and Surgical Diseases. *Arthur C. Allen.* New York, Grune & Stratton, 1951. 583 pages, 1115 illustrations. $15.00.

This book comprises the standard order of chapters on embryology, anatomy and physiology of the kidneys, uremia, malformations, diseases of glomeruli, of tubules, interstitial nephritis, pyelonephritis, tumors and histologic artefacts. The text is attractively printed and the illustrations are superb and surprisingly numerous. In fact, it is difficult at times to pursue the text between them; this is especially noticeable in the chapter on tumors.

The introduction sets the critical, somewhat iconoclastic tone of the entire volume. In his eager hunt for the truth, the author occasionally takes a shot at other hunters, but no one is seriously injured. He makes a sincere effort to integrate the viewpoints of pathologist, physiologist and clinician. The style is clear, direct, unvarnished and refreshing. The author's individual point of view is never left in doubt. He denies the existence of mesangium in the glomerulus and, therefore, of the intercapillary site of the specific lesions of diabetic glomerulosclerosis. His clarification and detailed discussion of glomerular diseases are lucid and provocative, and his development of the concept of the "membranous glomerulonephritis" for the nephrotic varieties sounds logical in these days of enhanced interest in the morphology and pathology of collagen. The various forms of "osmotic nephrosis" are excellently presented from both the pathologic and physiologic viewpoints. The concept of "lower nephron nephrosis" is at long last thoroughly criticized and relegated to its proper place. Sulfa nephropathy and the myeloma kidney are very well presented. The role of virus and rickettsial diseases in the production of focal glomerulonephritis and interstitial nephritis is emphasized. Diabetic glomerulosclerosis is considered absolutely specific for diabetes, while renal amyloidosis is assumed to be a nodular conversion of the collagen or reticulin in the walls of the capillaries. The vascular types of renal disease, including the rarer forms, are unusually well covered. The discussion of tumors is complete.

The only major criticism is that the title of the book is somewhat of a misnomer. The volume, however, is a noteworthy contribution to the pathology and pathogenesis of renal diseases, organic and functional. It will probably become a classic in its field.

LOUIS LEITER

Spatial Vector Electrocardiography. Clinical Electrocardiographic Interpretation. *Robert P. Grant and E. Harvey Estes, Jr.* Philadelphia, New York and Toronto, The Blakiston Company, 1951. 150 pages, 41 figures, $4.50.

This small book is not, as the authors point out in the preface, another textbook on electrocardiography, but is a presentation of a basic point of view or approach in electrocardiographic interpretation; namely, the meaning of surface leads in terms of electrical forces in the heart. It is an enlarged and revised edition of a monograph by the authors, published privately by Emory University in 1949.

The authors do not present a complicated instrumental method for the determination of spatial vectorcardiograms, but point out how these figures may be estimated, probably with fair accuracy, by inspection of conventional limb and precordial leads. The discussion and the concepts involved concerning the vectorcardiogram in the frontal plane are not, of course, new ones, since all experienced electrocardiographers view the limb leads in terms of what they mean relative to electrical forces in the heart.

To consider precordial leads as also due to a series of single vectors within the heart involves further assumptions and uncertainties largely due to the close proximity of chest electrodes to its anterior aspect. Nevertheless, the use by the authors of planes located by the position of the transitional complexes of QRS and T to assist in establishing the spatial orientation of the mean (or instantaneous) cardiac vectors is probably justified, and this is a new helpful approach to the interpretation of precordial leads.

Most of the chapters in the book present new ideas or new points of view relating to the interpretation of the ventricular complex, or parts thereof, as vector quantities. The material is logically presented, and the book is written in a clear and pleasing style. There are only a few statements in the entire book to which the reviewer objects, and it is obvious that the authors are fully conversant with the basic matters that underlie proper understanding and correct interpretation of conventional electrocardiograms. One wonders if such a background is not a necessary preliminary to the appreciation and intelligent use of the vector method.

This book is a good one and should be helpful to any physician who is seriously interested in electrocardiograms and their proper interpretation.

F. D. JOHNSTON, M.D.

Blood Clotting and Allied Problems. Transactions of the Third Conference. *Edited by Joseph E. Flynn.* New York, Josiah Macy, Jr., Foundation, 1950. 224 pages, 31 tables, 51 figures. $3.00.

The *Transactions* of the Conferences on Blood Clotting and Allied Problems held by the Josiah Macy, Jr., Foundation are records of informal discussion meetings of a group of active investigators, both clinical and laboratory, under the chairmanship of Irving S. Wright. The third conference centers around certain newer anticoagulants and methods for the control of anticoagulant therapy, but such meetings lead naturally to presentation of a diverse selection of material of current interest.

Phenylindanedione is a drug which has an action similar to that of dicumarol but one that is of much briefer duration; the same is true to a lesser extent of Tromexan. This may or may not be an advantage, depending on the plan of therapy to be followed. Jaques draws an analogy between the different dicumarol-like drugs and the different insulin preparations which vary in their duration of action. Paritol, a synthetic anticoagulant of the heparin type, is cheaper than heparin and has a more prolonged action, but occasionally produces severe allergic reactions.

By means of radioactive dicumarol, Jaques and his colleagues show that this drug is retained in the liver for a brief period; vitamin K seems to hasten its removal from this organ. A puzzling feature of these experiments is the fact that the effect on the prothrombin time increases as dicumarol leaves the liver, and that this effect reaches its peak after the drug is mostly gone. Whether or not this is due to the activity of metabolic products of dicumarol remains to be determined.

Brambel leads the discussion of the highly controversial topic of prothrombin tests. Evidence is brought forward that the prothrombin time does not measure prothrombin in the sense of the substance which is converted into thrombin and determines the yield of thrombin measured by the two-stage method. It is furthermore uncertain exactly what the prothrombin time does measure. Quick continues to regard the prothrombin time as a measure of prothrombin, but he defines prothrombin essentially in terms of the prothrombin time and without use of the criterion of measurable yield of thrombin. This disagreement on such a basic matter as the definition of prothrombin is sufficient indication of the complexity of the subject. At the same time, there is agreement as to the importance of the prothrombin time in the control of dicumarol therapy. Understanding of this test, and not of its mere mechanical performance, is needed for its intelligent use.

Prothrombin tests on serum are discussed by Brinkhous, Quick and Alexander, from their individual points of view. This work finds important practical application in the demonstration of the differences between normal and hemophilic serum, whatever the differences may be. Tocantins presents additional evidence on his own, equally interesting, approach to the study of hemophilia: the detection of an inhibitor of thromboplastin. A critical analysis of technics of the two-stage method is provided by Ferguson.

The application of zeta-potential measurements to the study of blood coagulation is reported by Wood.

Like the transactions of the two preceding conferences, this book has the most valuable feature of frank, informal exchange of opinion between research investigators, some of whom in their publications hardly seem even to speak the same language. Under these circumstances, the coherence and readability of the transactions are altogether remarkable, and are greatly to the credit of the editor.

FRANK D. MANN, M.D.

Angiocardiography as a Diagnostic Aid in Congenital Heart Disease. *J. W. C. deGroot.* Keesing, Amsterdam, 1951. 108 pages, 18 x-ray reproductions, 2 tables.

This report from the Department of Pediatrics and Child Health, University of Birmingham, England, as well as the University Clinic of Pediatrics at the University of Amsterdam, Holland, adds another book to the growing list of those concerned with angiocardiography, but unfortunately adds very little that is new. There are several typographical errors and the reproduction of the x-ray films, ordinarily one of the most interesting features in a study of this sort, are poor.

The first part of the book (29 pages) reviews the literature and provides a good bibliography. There is a discussion of the history of angiocardiography, a review of the various contrast media employed, as well as their dangers, and a brief description of some of the types of x-ray equipment used. The rest of the book deals with a description of the author's technic of accomplishing the examination as well as a summary of a few of his cases. With the apparatus available he was able to take two to four films per second. His study consists of 51 angiocardiograms on 45 patients, all with congenital cardiac lesions.

The book provides an easy-to-read, superficial introduction to the technics, indications for and results from angiocardiography as applied to congenital heart disease.

MILTON ELKIN

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SCIENTIFIC SESSIONS

Following are the titles of papers to be read at the Association's Scientific Sessions being held on Friday, April 18 and Saturday, April 19, at the Hotel Statler in Cleveland, Ohio:

First Session—9:00 a.m., Friday, April 18

Chairman, Louis N. Katz, President, American Heart Association

1. Observations on a Type of Congestive Failure Induced by Cortisone in Patients with Acute Rheumatic Carditis. Irving G. Kroop and S. R. Slater, Brooklyn, N. Y.
2. The Selection and Medical Management of Patients with Mitral Stenosis Treated by Mitral Commissurotomy. George C. Griffith, Los Angeles, Calif.
3. Right Auricular and Ventricular Pressure Patterns in Constrictive Pericarditis. Paul N. G. Yu, Frank W. Lovejoy, Jr., Howard A. Joos and Robert E. Nye, Rochester, N. Y.
4. Attempts at the Surgical Correction of Rheumatic Aortic Regurgitation. Charles P. Bailey, George D. Geckeler, William L. Likoff, Lowell L. Lane, Frank Massey, Harry Goldberg and H. Bolton, Philadelphia. Pa.
5. The Effect of Adrenocorticotropin and Cortisone upon Experimental Endocarditis and Glomerulonephritis. Robert N. Hammerstrom, C. Walton Lillehei, J. Donald Wargo and Maurice B. Visscher, Minneapolis, Minn.
6. The Use of Temporary Polyethelene Shunts to Permit Occlusions, Resection and Frozen Homologous Graft Replacements of Vital Vessel Segments. Creighton A. Hardin, Paul W. Schafer and E. Grey Dimond, Kansas City, Kans.
7. The Diagnostic Application of "Dye Dilution Curves" in Congenital and Acquired Heart Disease. James C. Broadbent, Robert G. Tompkins, Howard B. Burchell and Earl H. Wood, Rochester, Minn.
8. The Ventilatory Equivalent in Congenital and Acquired Heart Disease. Robert L. Grissom, Chicago, Ill.
9. LEWIS A. CONNER MEMORIAL LECTURE. The Nature of Cardiac and Pulmonary Dyspnea. Dickinson W. Richards, Jr., New York, N. Y.

Second Session—1:30 p.m., Friday, April 18

Chairman, Irving S. Wright, President-Elect, American Heart Association

10. Prevention of Myocardial Infarction with Long-Term Anticoagulant Therapy. E. Sterling Nichol and Joseph F. Borg, Miami, Fla.
11. The Present Status of Anticoagulant Therapy in Acute Myocardial Infarction. Henry I. Russek and Burton L. Zohman, Staten Island, N. Y.
12. Functional versus Organic Chest Pain: Differentiation by Dihydroergocornine (DHO-180). Arthur M. Master, Leon Pordy, Kenneth Cheskey, Charles I. Garfield, Sidney Storch and Isaac Goldstein, New York, N. Y.
13. The Production of Atherosclerosis in Monkeys by Dietary Means. George V. Mann, Anne McNally and Stephen B. Andrus, Boston, Mass.
14. The Use of Heparin in the Treatment of Severe Coronary and Peripheral Arteriosclerosis. Hyman Engelberg, Los Angeles, Calif.

15. Left Ventricular Hypertrophy: A Study of the Accuracy of Current Electrocardiographic Criteria when Compared with Autopsy Findings in 100 Cases. Ralph C. Scott, Vincent J. Seiwert, David L. Simon and Johnson McGuire, Cincinnati, Ohio.
16. Acute Hyponatremia due to Water Retention in Congestive Heart Failure. R. E. Weston, E. R. Borun, J. Grossman, H. A. Guerin, T. D. Ullmann, M. Wolfman and L. Leiter, New York, N. Y.
17. A New Surgical Concept in the Management of Refractory Cases of the Shoulder Girdle Syndromes. Jere W. Lord, Robert D. Huebner and Irving S. Wright, New York, N. Y.
18. PANEL DISCUSSION — Cardiovascular Therapeutics. E. Cowles Andrus, Chairman.

Third Session—9:00 a.m., Saturday
April 19

Chairman, Robert W. Wilkins, Council for High Blood Pressure Research

19. The Use of Protoveratrine in Hypertensive Emergencies and Chronic Hypertension. Edward Meilman, Boston, Mass.
20. Protoveratrine as a Treatment of Hypertensive Vascular Disease. J. H. Currens, G. S. Myers, J. S. McGinty and E. F. Bland, Boston, Mass.
21. The Ballistocardiogram in Coronary Artery Disease. William R. Scarborough, B. M. Baker, Jr., M. L. Singewald, F. W. Davis, Jr. and R. E. Mason, Baltimore, Md.
22. The Effects of Hexamethonium (C6) and Pentamethonium (C5) in Hypertensive and Normotensive Subjects. David Grob, Herbert C. Langford, Albert A. Kattus and Elliot V. Newman, Baltimore, Md.
23. Observations on the Hemodynamics of Mitral Stenosis in Man Compared with Chronic Experimental Mitral Stenosis in Dogs. G. H. A. Clowes, Jr., Salvatore M. Sancetta and Donald B. Hackel, Cleveland, O.
24. Experiences with New Depressor Drugs before and after Subtotal Adrenalectomy Alone or Combined with Sympathectomy. Joseph H. Hafkenschiel, William A. Jeffers, M. August Lindauer, Harold A. Zintel, Peter T. Kuo, Carl K. Friedland, David P. McCallie, A. Gorman Hills and Charles C. Wolferth, Philadelphia, Penna.
25. An Experimental Consideration of Atherogenesis. Silas M. Evans, Harry K. Ihrig, James A. Means, Walter Zeit, and Eugene E. Haushalter, Milwaukee, Wis.
26. The Pathogenesis of Spontaneous Myocardial Rupture. Stanford Wessler, Paul M. Zoll and Monroe J. Schlesinger, Boston, Mass.
27. GEORGE E. BROWN MEMORIAL LECTURE. Physiological Considerations Concerned with the Pathogenesis and Treatment of Obstructive Vascular Disease. Isaac Starr, Philadelphia, Pa.

Fourth Session—1:30 p.m., Saturday, April 19

Chairman, Hugh Montgomery, Section on Circulation

28. A Comparison of the Changes in Salt and Water Excretion and in Renal Hemodynamics during Induced Congestion of the Superior and Inferior Venae Cavae of Man. Saul J. Farber, William H. Becker and Ludwig W. Eichna, New York, N. Y.
29. Occlusive Hepatic Venous Catheterization in the Study of Portal Hypertension. J. D. Myers and W. Jape Taylor, Durham, N. C.
30. Cerebral Hemodynamic and Hypotensive Effect of Intravenous Veriloid Administered to Patients with Severe Hypertensive Disease. John H. Moyer, Houston, Tex.
31. A Method for Studying the Capillary Filtration Rates of Water and Electrolytes with Preliminary Observations. Edward D. Freis and Thomas F. Higgins, Washington, D. C.

32. The Control of Arterial Hypertension. Henry A. Schroeder, St. Louis, Mo.
33. Hypercholatemia: Its Causal Relationship to Hypercholesteremic States. Ray H. Rosenman, Meyer Friedman and Sanford O. Byers, San Francisco, Calif.
34. Cardiovascular Cineradiography: A Practical Method for Diagnosis and Teaching. James V. Warren, Heinz S. Weens and Frank E. Morgan, Jr., Atlanta, Ga.
35. Pulmonary and Renal Circulatory Dynamics in Patients with Beriberi Heart Disease before and after Thiamine Therapy. Harper K. Hellems, Henry S. M. Uhl, Lloyd T. Iseri, George O. Clifford, Leonard Leight and Gordon B. Myers, Detroit, Mich.
36. Participation of the Renal Pressor System in Hypertensive Vascular Disease. Georges M. C. Masson, Cleveland, O.
37. The Hemodynamics of Shock Accompanying Myocardial Infarction. Warren W. Smith and Arthur C. Fox, New York, N. Y.
38. Cerebral Vascular Reactivity to Carbon Dioxide in Cerebral Arteriosclerosis, Senility and in Normal Subjects during Anesthesia. James F. Schieve and William P. Wilson, Durham, N. C.

EXPERIMENTAL PROGRAM

Basic Science Sessions

Following are the titles of papers to be read at the Association's Basic Science Sessions, being held on Saturday, April 19 (running concurrently with the General Scientific Sessions):

First Session—9:00 a.m., Saturday, April 19

Chairman, Carl J. Wiggers

39. Needle Biopsy of the Heart for Biochemical Studies in the Intact Unanesthetized dog. Gus G. Casten and Julian B. Marsh, Washington, D. C.
40. Nucleotide Metabolism in Cardiac Activity. Philip A. Khairallah, Durham, N. C.
41. Elementary Reactions in Contractile Activity. W. F. H. M. Mommaerts, Durham, N. C.
42. Cardiac Effects of Some Drugs Which Produce Ventricular Fibrillation in Conjunction with Adrenaline. F. N. Fastier, J. Belford, H. M. Wosko and C. McC. Brooks, New York, N. Y.
43. Effects of Oxygen at High Tension upon Rapid Ventricular Tachycardia and upon Blood Pressure in Dogs with Acute Myocardial Infarction. A. Sidney Harris, Roy W. Olsen, Antonio Estandia and Tedroe J. Ford, Jr., Houston, Texas.
44. The Interrelations of Pulmonary Arterial, "Capillary," and Left Atrial Pressures under Experimental Conditions. Jay L. Ankeney, Cleveland, Ohio.
45. Functional and Anatomical Study of the Vasomotor Innervation of the Footpad of the Dog. W. C. Randall, W. F. Alexander, J. W. Cox, F. E. Franke, A. B. Hertzman, St. Louis, Mo.
46. Cutaneous Vascular Responses to Rising Environmental Temperature. A. B. Hertzman, W. C. Randall, H. E. Ederstrom and C. N. Peiss, St. Louis, Mo.

Second Session—1:30 P.M., Saturday, April 19

Chairman, Carl J. Wiggers

47. Continuous Recording of Systemic Blood Flow in the Dog by Means of the Potter Electro-Turbinometer. Stanley J. Sarnoff and Erik Berglund, Boston, Mass.
48. Studies on the Aorta to Coronary Sinus Anastomosis of Beck. R. W. Eckstein, Carl Hornberger, George Smith and David Leighninger, Cleveland, Ohio.
49. The Transplanted Heart and Its Behavior. A. A. Luisada, E. Marcus and S. N. T. Wong, Chicago, Ill.

50. Frequent Determination of Cardiac Output by the Fick Principle Excluding Gas Analysis. J. Grossman, R. E. Weston, E. R. Borun, A. S. Buchberg, L. Hallinger, H. Mark and L. Leiter, New York, N. Y. .
51. Treatment of Experimental Hypertensions with Renin and with Antirenin. G. E. Wakerlin, R. B. Bird, B. B. Brennan, M. H. Frank, E. Henrioulle, S. Kremen, I. Kuperman and J. H. Skom, Chicago, Ill.
52. Quantitative Circulatory Responses to an Acute Anoxemia Test in Dogs with Progressive Experimental Coronary Narrowing. E. L. Foltz, W. F. Sheldon, R. G. Page, J. J. Sayen and W. T. Fitts, Philadelphia, Pa.
53. The Resistance of Hearts with Coronary Occlusion to Anoxia. Albert Hurlimann, Cleveland, Ohio.
54. Effect of Arteriovenous Fistula on the Circulation. Rene Wegria, Charles W. Frank, Hseuh H. Wang and Robert Miller, New York, N. Y.
55. Experimental Heart Failure in Dogs with Arteriovenous Fistulae. J. R. R. Bobb, C. W. Lillehei and M. B. Visscher, Philadelphia, Pa., and Minneapolis, Minn.
56. Kinetic Factors in the Progression of Vascular Stenosis. Simon Rodbard, Chicago, Ill.
57. The Effect of Increased Right Ventricular Work on the Electrocardiogram. A Comparsion of the Effects of Congenital Heart Disease and Mitral Stenosis. Richard S. Cosby, Los Angeles, California.
58. Correlation of Electrocardiogram with Right Ventricular Hypertension and Absolute and Relative Right Ventricular Work. Richard W. Watts, Herman K. Hellerstein, Bernard L. Brofman, Walter H. Pritchard and Douglas J. Moore, Cleveland, O.

ANNUAL MEETING

The chief speaker at the Association's Annual Dinner on Friday, April 18, will be Dr. Claude Forkner, official physician to the Shah of Iran and a member of the Medical Advisory Board of the Iran Foundation. Dr. Forkner's topic will be, "Iran is Ill—A Physician's Consultation." Dr. Forkner is Associate Professor of Clinical Medicine at Cornell University and Associate Attending Physician at New York Hospital.

The Annual Meeting will begin on Thursday, April 17, with a meeting of the Assembly which will include panel discussions, reports and elections. Special reports on heart association programs and a panel discussion between physicians and members of the press will be presented concurrently with the Scientific Sessions, on Friday, April 18. The Annual Meeting of the Scientific Council will take place on the last day of the sessions, Sunday, April 20.

COUNCIL FOR HIGH BLOOD PRESSURE RESEARCH

The Association's Council for High Blood Pressure Research will hold its Annual Meeting at the Hotel Cleveland in Cleveland on May 23 and 24.

A. W. Robertson, Chairman of the Board of the Association, will be the principal speaker at the Council's Annual Dinner on May 24th.

ANIMAL EXPERIMENTATION

The statement on the subject of animal experimentation, as it appeared in the Proceedings of the First National Conference on Cardiovascular Diseases, has been adopted by the Executive Committee of the Board as the official policy of the Association. The Conference was held in Washington, D. C., in January, 1950.

The statement reads: "The necessity for animal experimentation has been abundantly established on the basis of the fact that most of the great discoveries to improve human health of the past fifty years have been at least in part the direct result of animal studies. It should further be pointed out that most of the progress in the saving of animal lives has also resulted from animal experimentation. Animal studies under humane conditions should therefore be made available and encouraged wherever they may contribute to human or animal welfare.

As one means to this end it is important that unwanted stray animals now generally destroyed in public pounds be made available to accredited institutions and that the policies of the National Society for Medical Research be strongly endorsed and supported."

CENTRAL OHIO FELLOWSHIP

The Central Ohio Heart Association is continuing a one-year Fellowship at Ohio State University College of Medicine. The basic requirements are: Graduation from a recognized medical college, one year rotating internship, two years residency in medicine, and one year residency in cardiology. The Fellowship stipend is $4,800 per annum, to start on July 1, 1952. Applications should be sent to Dr. R. W. Kissane, 9 Buttles Avenue, Columbus, Ohio, before May 1.

INTERAMERICAN CONGRESS

The following have been designated as official delegates of the Association to the Fourth Interamerican Cardiological Congress to be held in Buenos Aires from September 1–6, 1952: John Hepburn, M.D., Toronto; George R. Herrmann, M.D., Galveston; Louis N. Katz, M.D., Chicago; Myron Prinzmetal, M.D., Beverly Hills, Calif.; Howard B. Sprague, M.D., Brookline, Mass.; Paul D. White, M.D., Boston; Carl J. Wiggers, M.D., Cleveland; and Irving S. Wright, M.D., New York.

EUROPEAN CONGRESS OF CARDIOLOGY

The First European Congress of Cardiology will be held in London, England, from September 9–12, 1952. The Congress is being organized by the British Cardiac Society, in collaboration with the Presidents of the European Society of Cardiology. Sir John Parkinson will serve as Chairman. The Congress will be held at the University of London, Bloomsbury, W.C.1. Papers will deal with diseases of the heart and vascular system and their treatment. Inquiries should be addressed to the Secretary of the Congress, Dr. K. Shirley Smith, Institute of Cardiology, 35 Wimpole Street, London, W.1.

MEXICAN SOCIETY OF CARDIOLOGY

The newly elected officers of the Mexican Society of Cardiology are: President, Dr. Demetrio Sodi Pallares, Vice President, Dr. Luis Mendez; Treasurer, Dr. Armando Cuellar; and Secretary, Dr. Felipe Mendoza.